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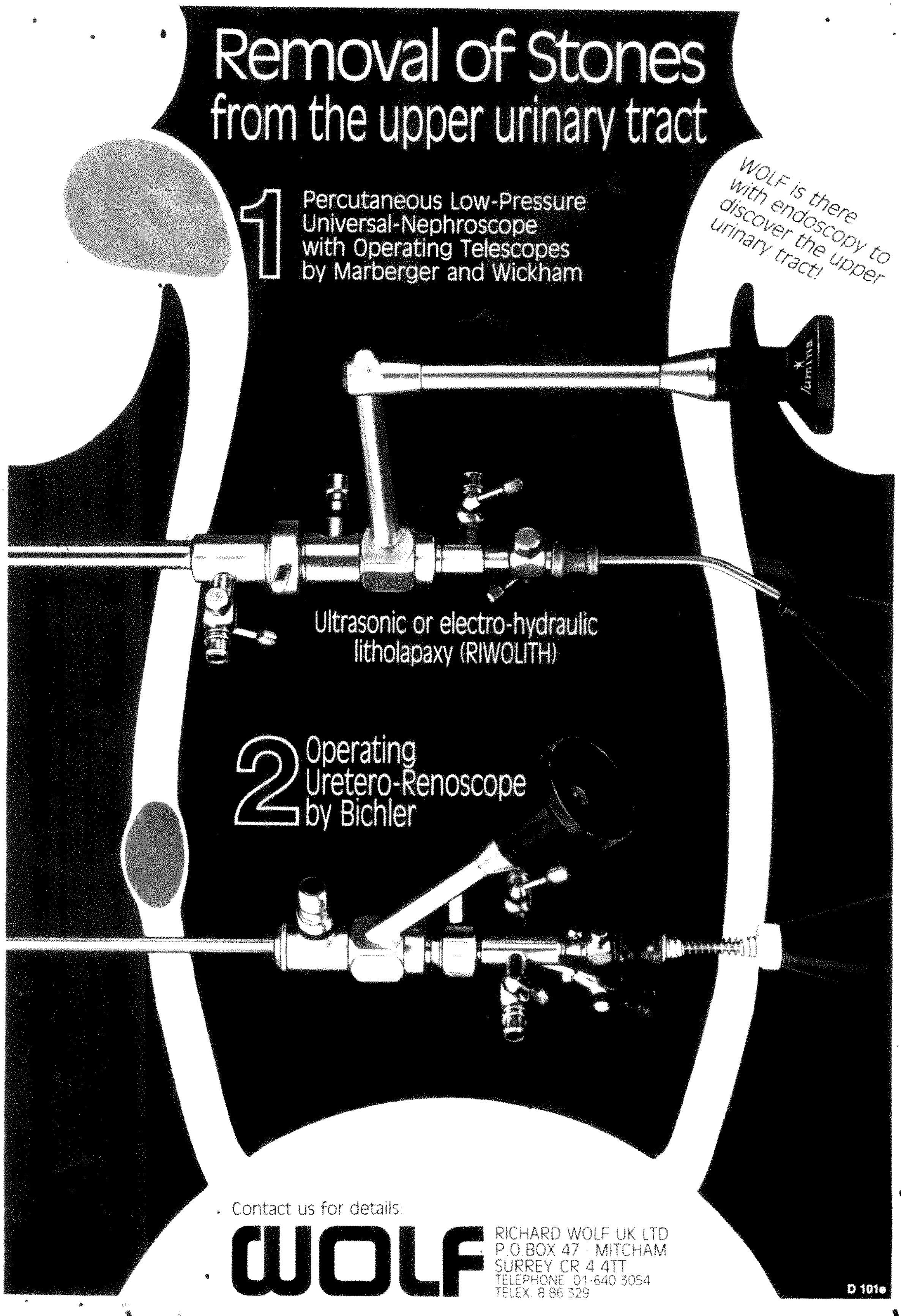

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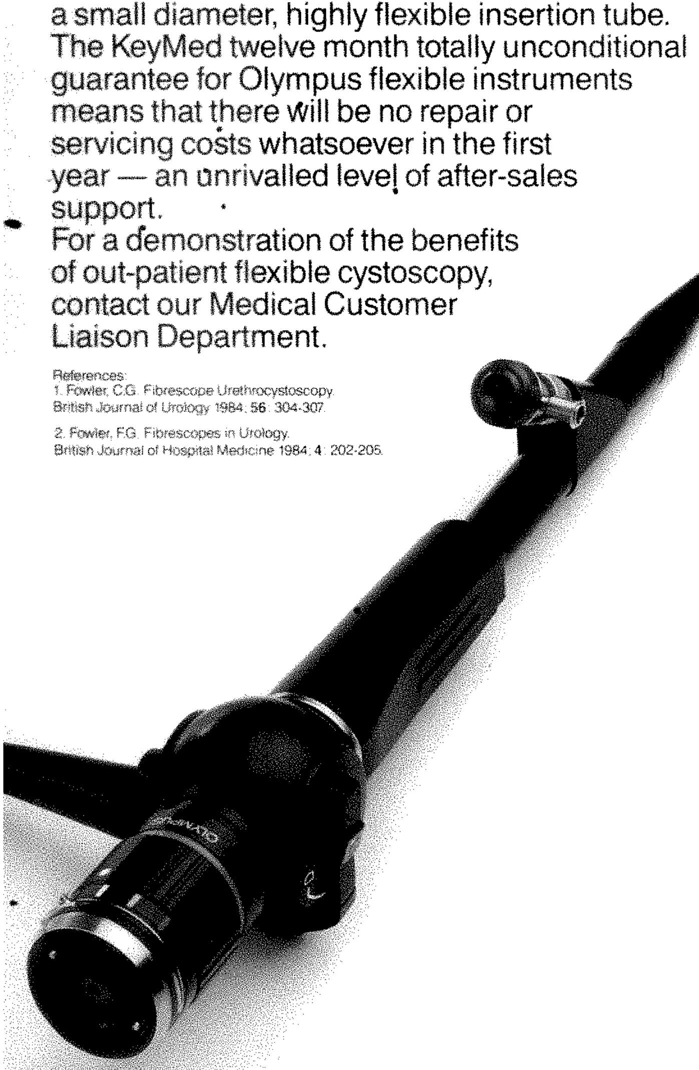

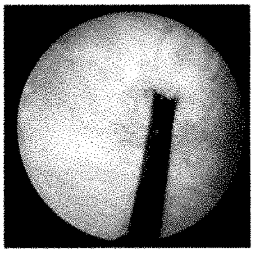

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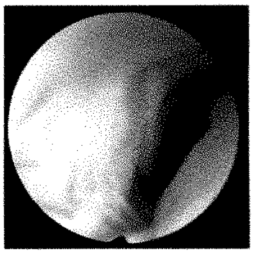

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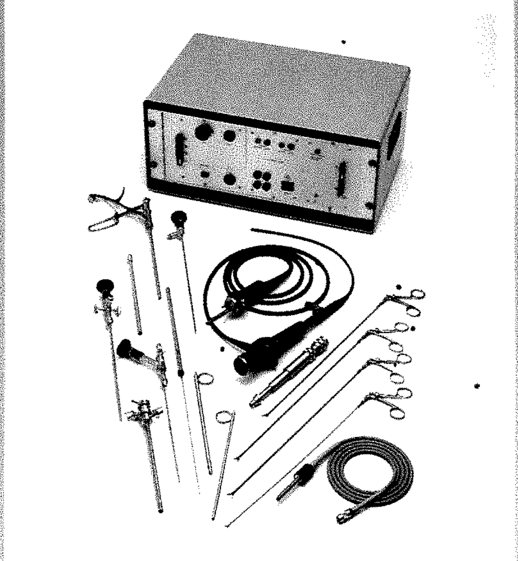

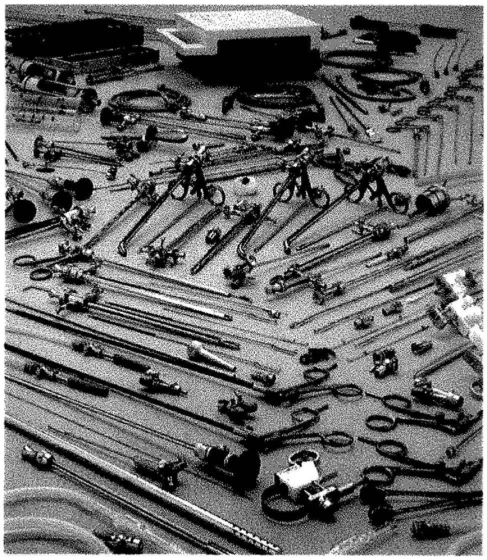

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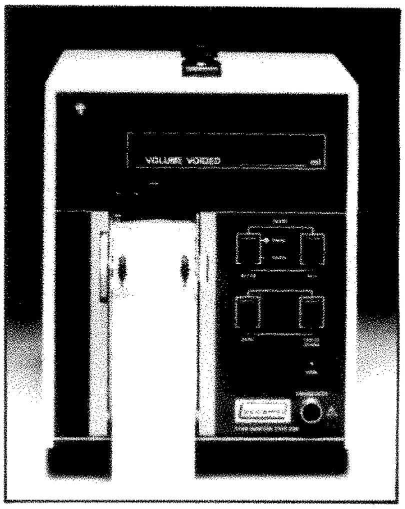

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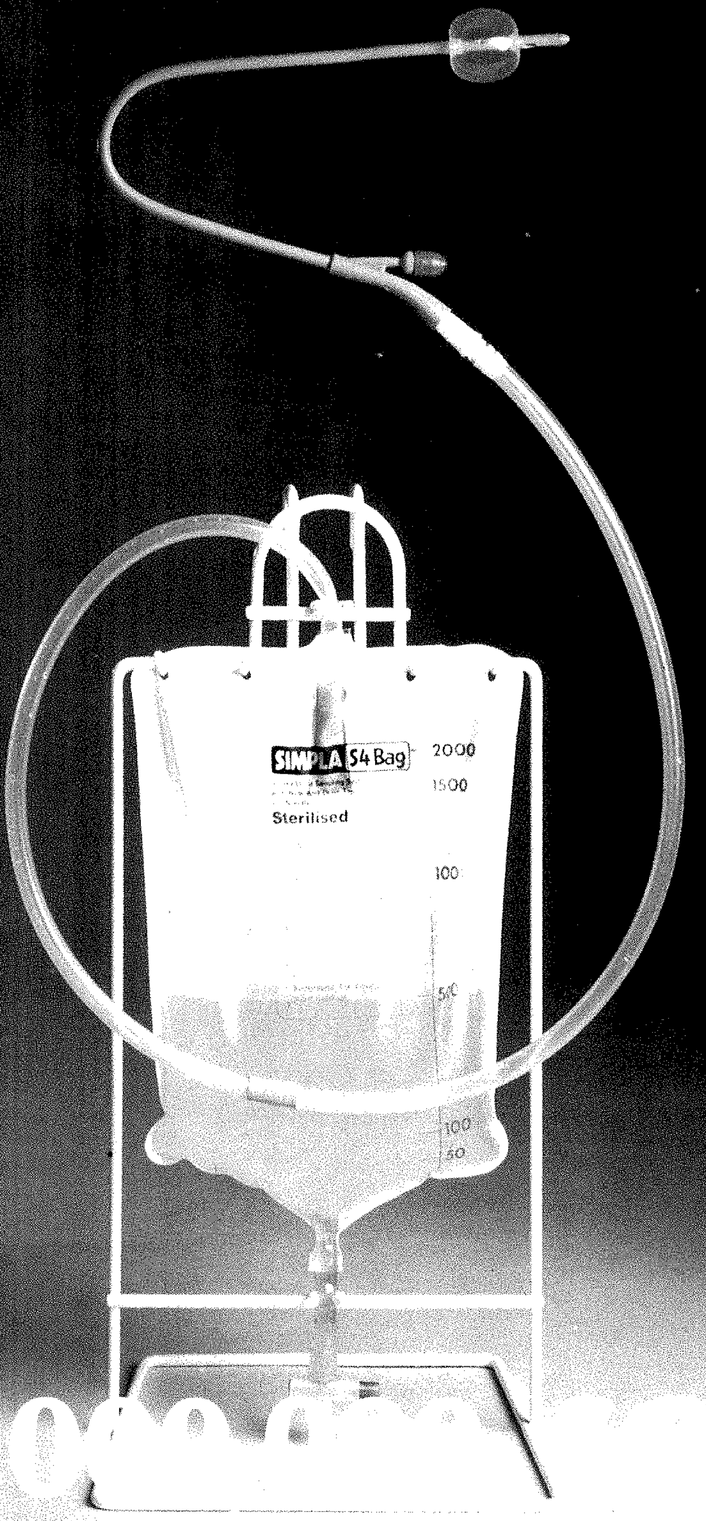

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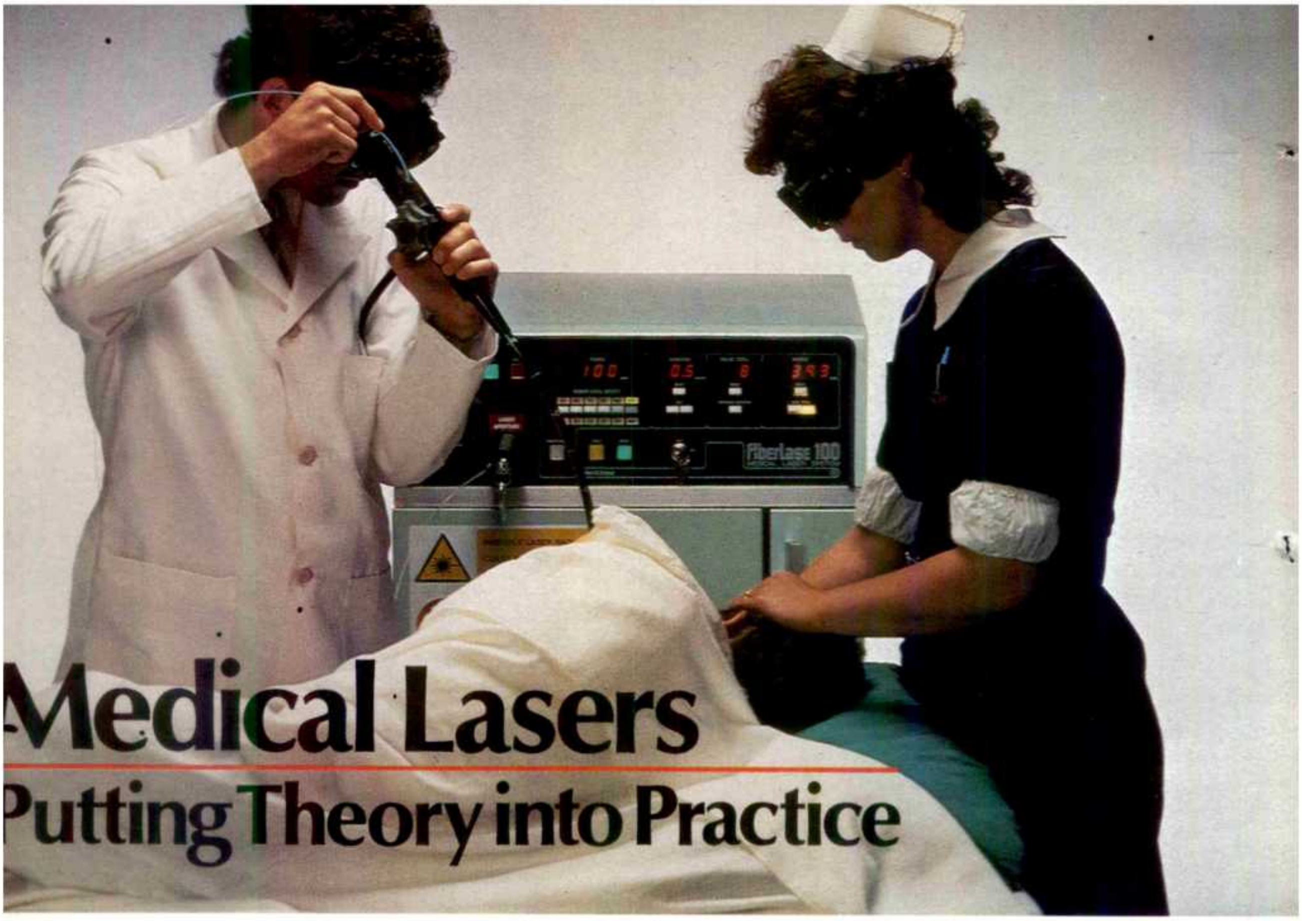

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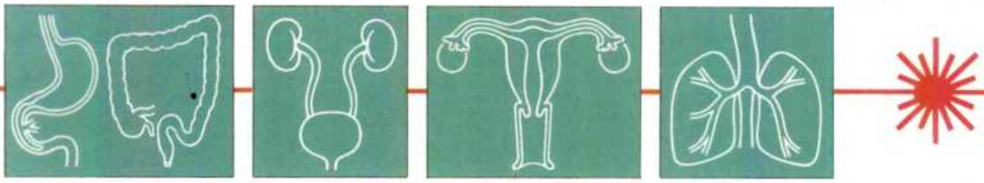

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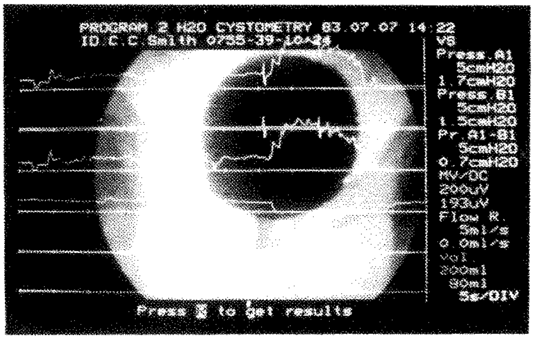

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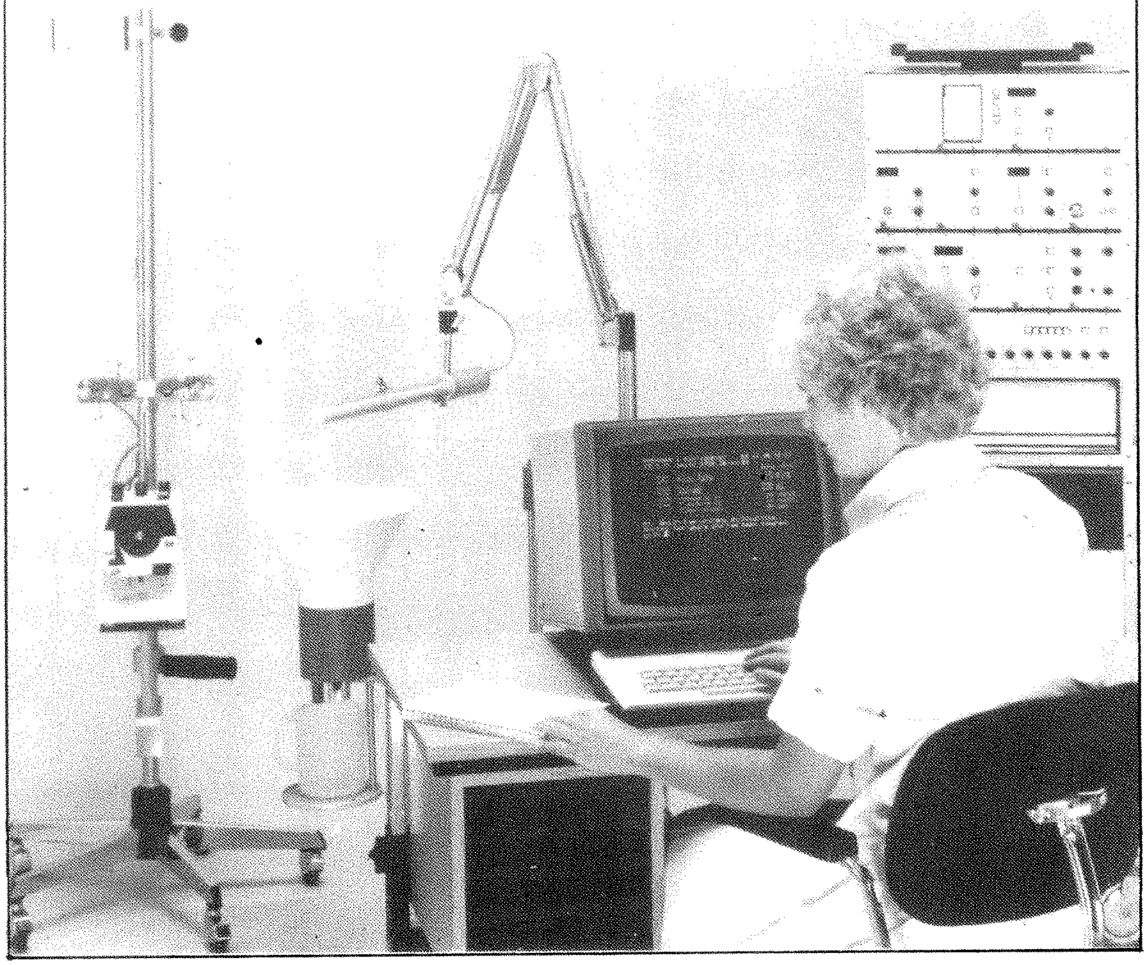

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Diuresis and Renal Functional Recovery in Chronic Retention

M. C. BISHOP

Department of Urology, City Hospital, Nottingham

Summary—Fifty-five patients with chronic urinary retention and incipient or actual renal failure were studied. In the majority of patients renal function improved after bladder decompression, irrespective of whether or not a diuresis occurred. Excessive loss of salt and water was rarely a matter of concern and most patients did not require intravenous fluid replacement. Several lost weight and experienced a fall in blood pressure during the period of diuresis without adverse effect upon renal functional recovery. A profound fall in blood pressure occurred in only three patients, all of whom required long-term sodium supplementation. It is concluded that the problem of salt and water loss after bladder decompression in patients with renal failure is exaggerated and difficult to predict. Over-enthusiastic replacement of fluid in strict accordance with output could readily lead to fluid overload and prolongation of the diuretic period. Therefore fluid replacement should be determined by the clinical condition of the patient and measurement of improving renal function with less emphasis on urine output and its electrolyte content.

Most clinicians are aware that chronic bladder neck obstruction can lead to bilateral hydronephrosis and renal failure. Relief of obstruction will usually result in at least partial recovery of renal function, often with a salt and water diuresis (Goodwin, 1976). It is desirable that the patient should have recovered from this phase before prostatic surgery is contemplated because an obligatory diuresis will add considerably to the problems of peri-operative fluid balance. Furthermore, surgical trauma is best withstood when renal function is optimal (Beck, 1970). It is therefore important that the extent of the diuretic response and likely degree of renal functional recovery can be forecast in selecting the appropriate time for operation.

For practical purposes it is often assumed that a diuresis after catheterisation implies that there is potential for functional recovery and that its degree is related to the rate of improvement after decompression. Conversely, there are less grounds for optimism in the absence of a diuresis. These assertions have been re-examined in the present study.

Patients and Methods

Fifty-five patients (mean age 71 years, range 52-89) with painless bladder distension were studied. They comprised approximately 20% of all patients undergoing transurethral resection for benign or malignant prostatic obstruction in the course of 18 months. They were selected on a basis of either elevation of plasma creatinine (> 120 µmol/l) and/or upper tract dilatation (hydroureter and hydronephrosis) on intravenous urography. Those with chronic retention but normal calibre ureters and unimpaired function were excluded. Forty-seven patients had elevated plasma creatinine. A further eight patients had normal plasma creatinine but upper tract dilatation.

Symptoms

Thirty per cent of the group presented with urinary incontinence, 60% with minimal or mild prostat-

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Accepted for publication 27 July 1984.

ism and only 10% with symptoms which would, in the absence of chronic retention, have otherwise justified prostatectomy. Only one patient presented with acute-on-chronic retention.

Physical Signs

Eighteen patients (32%) had oedema of the legs or genitalia, which was not accompanied by other signs of congestive cardiac failure and which quickly resolved after catheterisation. Several patients had received diuretics before admission because of these symptoms. In two cases the distended bladder appeared to tilt to one side of the abdomen and the leg oedema was more severe on that side. Approximately 50% had a diastolic blood pressure in excess of 95 mm Hg.

Forty-one patients underwent intravenous urography. All had upper tract dilatation and in a few cases this too was asymmetrical and misleading so that further investigations were undertaken on the unilaterally poorly functioning kidney. The remaining patients who did not undergo urography were assumed to have obstructive renal failure.

All patients were catheterised. In the majority the residual urine (mean volume 1.43 litres, range 600-3100 ml) was drained immediately and thereafter daily measurements of body weight, blood pressure, plasma creatinine, sodium, potassium and 24-h urine volume taken. A diuresis was arbitrarily defined as urine output in excess of 3 l/24 h.

Results

Relationship between Diuresis and Renal Failure

Twenty-nine patients (52%) had a period of diuresis (mean maximum output/24 h 5.5 litres, range 3–12; mean duration 4.8 days, range 1–13). Twenty-seven of the 47 patients (57%) with elevation of plasma creatinine (>120 μmol/l) and 2 of 8 patients with normal function had a diuresis. The relationship between renal failure and maximum output after catheterisation of >3 litres was not significant ($\chi^2 = 2.89$, $P = 0.09$).

The degree of diuretic response was related neither to the initial plasma creatinine concentration (Fig. 1) nor to the maximum rate of fall in plasma creatinine which invariably occurred in the first 48 h (Fig. 2). The diuretic response had no significant relationship with recovery of function (Table, $\chi^2 = 2.67$, $P = 0.26$) and a normal urine output was quite consistent with improvement, which was often dramatic (Figs 3 and 4).

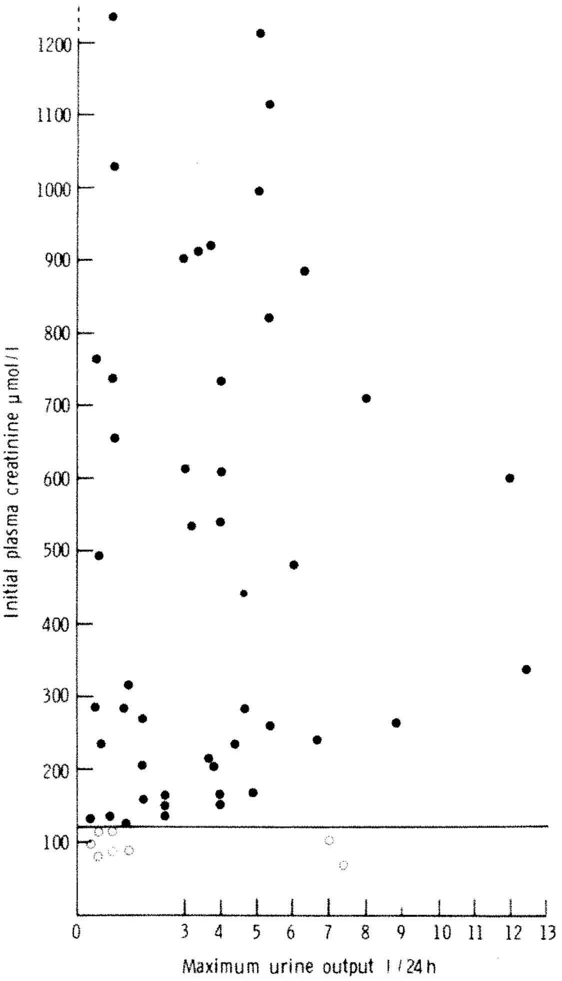

Fig. 1 Relationship between initial plasma creatinine and maximum urine output.
● initial plasma creatinine elevated.
○ initial plasma creatinine within normal limits.

Table Diuretic Response and Recovery of Renal Function

	Diuresis	*No Diuresis*
Recovery of renal function		
None	3	6
Partial	16	9
Complete	8	5
Total	27	20

Hyponatraemia and Intravenous Fluid Replacement

In 12 patients plasma sodium fell after catheterisation. Two patients in this group had no diuresis and one had normal plasma creatinine. In 8 patients

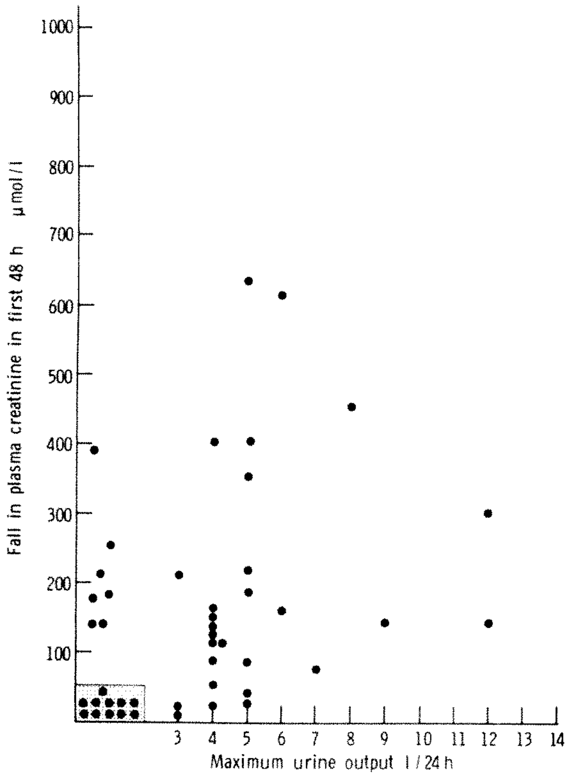

Fig. 2 Relationship between fall in plasma creatinine in the first 48 h after decompression and maximum urine output. Shaded area represents absent diuresis and no fall in plasma creatinine.

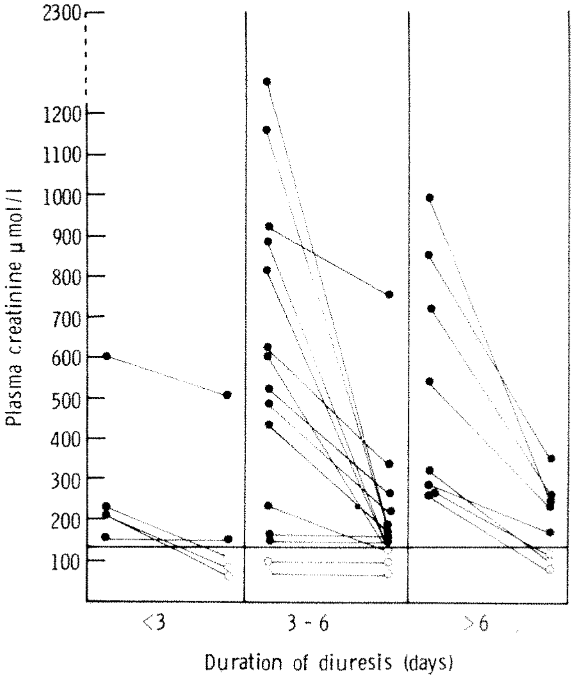

Fig. 4 Fall in plasma creatinine (initial to final stable level) in relation to duration of diuresis.

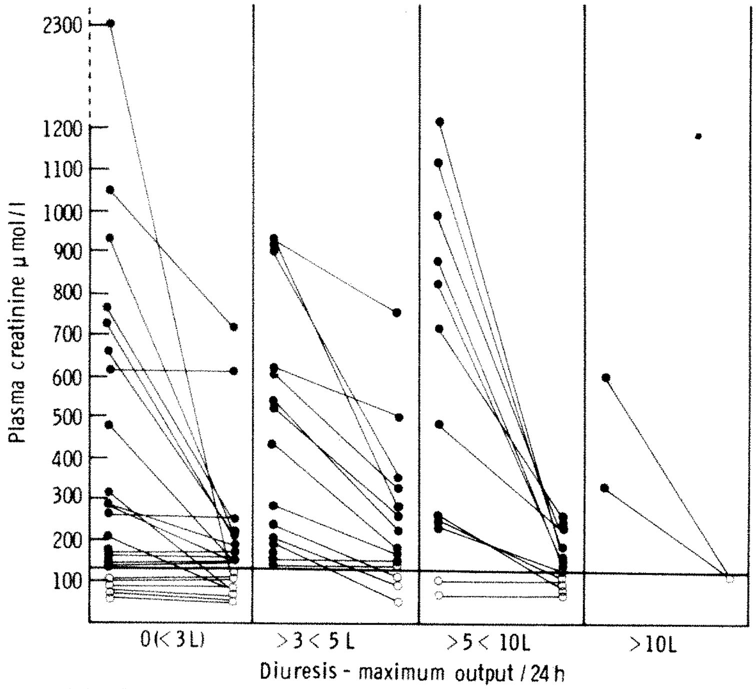

Fig. 3 Fall in plasma creatinine from initial to final stable level in relation to maximum urine output after decompression.

hyponatraemia was trivial (132-134 mmol/l) but 4 required intravenous sodium replacement because of more marked hyponatraemia and 3 of them were ultimately regarded as chronic salt losers for whom long-term oral sodium supplementation was required. Before the intravenous infusion was administered these patients showed a considerable fall in blood pressure with postural hypotension.

Six other patients without hyponatraemia were given intravenous fluid replacement on the basis of high initial urine output. In one case this led to an exacerbation of congestive cardiac failure. In retrospect, intravenous replacement was probably unnecessary.

In 13 patients, diuresis led early on to weight loss. In 5, hyponatraemia developed and in 3 others blood pressure fell, so that intravenous saline supplements were required. The remaining 8 patients with normal plasma sodium concentration were treated without intravenous fluids and allowed to lose weight (mean loss 4.4 kg, range 2-7) with diuresis after catheterisation. None became clinically salt and water depleted, although the blood pressure fell in 4 patients. However, the final level was acceptable (>70 mm Hg diastolic) with no additional postural drop. In all such patients for whom intravenous fluids were withheld, plasma creatinine fell wherever it was elevated initially.

Blood pressure fell in 55% of patients who experienced a diuresis and in 25% of those with a normal urine output.

Weight of Resected Prostatic Tissue

The weight of prostatic tissue resected transurethrally ranged from 4 to 190 g. The distribution was similar to that obtained from all patients undergoing prostatic surgery.

Discussion

This survey was carried out on patients with chronic urinary retention in whom urgent treatment was thought necessary on account of actual or incipient renal failure. They formed approximately 20% of the total number of patients admitted for prostatic surgery during an 18-month period. This proportion is similar to that described in previous studies (Beck, 1970). In the majority, the plasma creatinine was elevated because of bladder outflow obstruction and the remainder had upper tract dilatation on urography. According to recently published data, two groups of patients with chronic retention can be distinguished urodynamically on a basis of high and low bladder pressure during filling cystometry (Abrams *et al.*, 1978; George *et al.*, 1983). The group with high pressure are at risk of developing obstructive nephropathy. All patients presently described could therefore have been classified in this group, although urodynamic data are not presented here. Typically for the high pressure group, most patients had rather minimal symptoms of bladder outflow obstruction and several presented with incontinence. Peripheral oedema was common and seemed to be due to pelvic venous compression by the enlarged bladder; sometimes it was asymmetrical. Urographically, ureteric dilatation was also occasionally asymmetrical and this caused diagnostic confusion.

Previous studies have been vague on how to predict the incidence and extent of the obligatory diuresis in obstructive uropathy after bladder decompression. Eiseman *et al.* (1955) indicated that negative sodium and water balance commonly occurs and subsequent clinical and investigative studies have shown that a diuresis, of varying degrees, is invariable (Chisholm, 1982; George *et al.*, 1983). It has often been implied that it should be expected in all patients with recoverable elevation of the plasma creatinine. In the present study a diuretic response occurred in only 52% of the whole group and was absent in many patients with renal failure. Whilst a diuresis was usually associated with at least some recovery of function, plasma creatinine also fell, often from a very elevated initial level, with a normal urine volume.

Diuresis after decompression in obstructive uropathy is not unlike that which occurs during the early phases in recovery from acute tubular necrosis. The causes can be summarised as clearance of an osmotic load (Maher *et al.*, 1963), tubular functional inadequacy (Bricker *et al.*, 1957; Witte *et al.*, 1964) and release of an accumulated surplus of fluid and electrolytes. It is clear that much of the polyuria is only evacuation of excess extracellular fluid and over-enthusiastic attempts to replace it prolong the diuresis and lead to over-hydration (de Wardener, 1967). Many of our patients were oedematous and hypertensive and a period of negative fluid balance after catheterisation, shown by weight loss and moderate fall in blood pressure level, was clearly desirable; this was achieved without prejudice to renal perfusion and hence to improvement in function. It must be acknowledged that hyponatraemia associated with diuresis did occur in some patients, but it was rarely symptomatic and could usually be managed without parenteral sodium replacement. The small number of patients with a salt-losing nephropathy were easily identified by a rapid fall in plasma sodium and postural hypotension.

In the management of high pressure chronic retention, prompt decompression of the bladder is clearly necessary. The extent and duration of a subsequent diuresis are hard to predict and in particular are not related to elevation of the plasma creatinine. Even severely impaired renal function can return rapidly towards normal without excess fluid loss. Routine intravenous fluid replacement is unnecessary and should be determined by the clinical condition of the patient and by observation of steady improvement in renal function, rather than by slavish attention to the urine output and its electrolyte content.

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The Author

M. C. Bishop, FRCS, Consultant Urological Surgeon, Department of Urology, City Hospital, Hucknall Road, Nottingham NG5 1PB.

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Predictive Value of Pressure Flow Studies for the Functional Outcome of Reconstructive Surgery for Hydronephrosis

J. C. DJURHUUS, S. S. SØRENSEN, T. M. JØRGENSEN and F. TAAGEHØJ-JENSEN

Institute of Experimental Clinical Research, University of Aarhus; Urological Department K and Division of Nuclear Medicine, Aarhus Municipal Hospital, Denmark

Summary—In 22 of 40 patients with unilateral hydronephrosis the pressure flow study was compared with the outcome of surgery. Seventeen of the 22 patients had impaired function before surgery as judged from the 2-min uptake on the renogram. The pressure flow study as a measure of pre-operative obstruction showed no relation to the functional outcome of surgery. Patients with obstructed pressure flow studies as well as those without signs of obstruction either remained stable or improved after surgery.

It was concluded that pressure flow studies are of no value in predicting the outcome of surgery for hydronephrosis.

The policy for treatment of idiopathic hydronephrosis has changed tremendously since Trendelenburg performed the first reconstruction in 1886. Following the counterbalance theory of Hinman (1922), which led to the widespread use of nephrectomy, the general trend is now towards reconstructive surgery rather than nephrectomy.

The increased use of IVU radionuclides and ultrasonic investigations has led to the diagnosis of an increasing number of almost symptomless cases of idiopathic hydronephrosis without secondary complications. At the same time a few studies on the spontaneous course of the disease (Bratt *et al.*, 1977) have revealed that most of these selected patients show no progression of the disease. Predictive pre-operative diagnostic procedures revealing ongoing significant obstruction are therefore highly relevant.

In 1973 Whitaker advocated the use of a constant perfusion pressure flow study to distinguish between obstructed and non-obstructed congenital dilatations. Borderlines between obstructed and non-obstructed responses were outlined (Whitaker, 1979) and the results of follow-up in patients categorised according to the pressure flow test were reported (Witherow and Whitaker, 1981).

We have previously shown that the degree of hydronephrosis and the decrease in renal function bear no relation to the pressure flow study (Djurhuus *et al.*, 1982). The present report concerns the relationship between the pre-operative pressure flow study and the functional outcome after surgery for hydronephrosis.

Patients and Methods

Forty patients with urographically verified unilateral hydronephrosis were referred for treatment. Excluded from the investigation were two patients with single kidney hydronephrosis, three in whom the perfusion test did not succeed, eight who were lost to follow-up and five who underwent nephrectomy. Thus the group comprised 22 patients, 9 females and 13 males, with a mean age of 27.2 years (range 3-67). All underwent isotope renography performed either conventionally or as a gamma camera investigation. The isotope used was ^{131}I Hippuran or ^{123}I Hippuran. The 2-min uptake fraction was used for estimation of function. Renography was repeated 6 and 12 months after

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operation. All of the patients underwent an Anderson-Hynes pyeloplasty (Anderson and Hynes, 1949) and before proceeding to the reconstruction an intra-operative pressure flow test was performed. The pelvis was visualised but not dissected free. Two 4F catheters were inserted into the pelvis and secured by a purse-string suture. A pressure transducer (Siemens, strain gauge 746) was connected to one of the catheters and adjusted at the level of the kidney, and the baseline pressure was then measured over a period of 10 min.

The other catheter was connected to a roller pump adjusted to a flow of 8 to 10 ml/min. Perfusion was started and interrupted when the pressure levelled out or exceeded 30 to 40 cm H_2O. Throughout the procedure the bladder was drained and the wound edges kept together.

Analysis was made of baseline and maximal pressures during constant perfusion. The borderlines for pathological and equivocal responses were determined according to Whitaker (1979). On the control renograms, increases and decreases of more than 10% of the total 2-min uptake were considered a significant change.

Results

The renograms showed that 17 patients had a functional share of 40% or less on the hydronephrotic side. They were equally distributed over the whole range of decreased functional shares (Table).

Table Renographic Share of Function Before and Gain After Surgery for Hydronephrosis

Functional share	*Number of patients*	*Gain in function Number of patients*	*Pressure flow category**
≤10	3	2	I, III
10–20	5	3	I, I, II
21-30	5	1	III
31-40	4	2	III, III
41-50	5	—	—

* Whitaker (1979).

The outcome of the pressure flow study is shown in Figure 1. Twelve patients showed an obstructed, high pressure response during perfusion, 4 had an intermediate response, and 6 showed a non-obstructed low pressure response.

Six months after reconstruction 3 patients showed a significant decrease in function and 10 had a significant increase. Patients with decreased function at 6 months showed some restoration after 12 months, whereas those with increased function either stabilised or continued to progress.

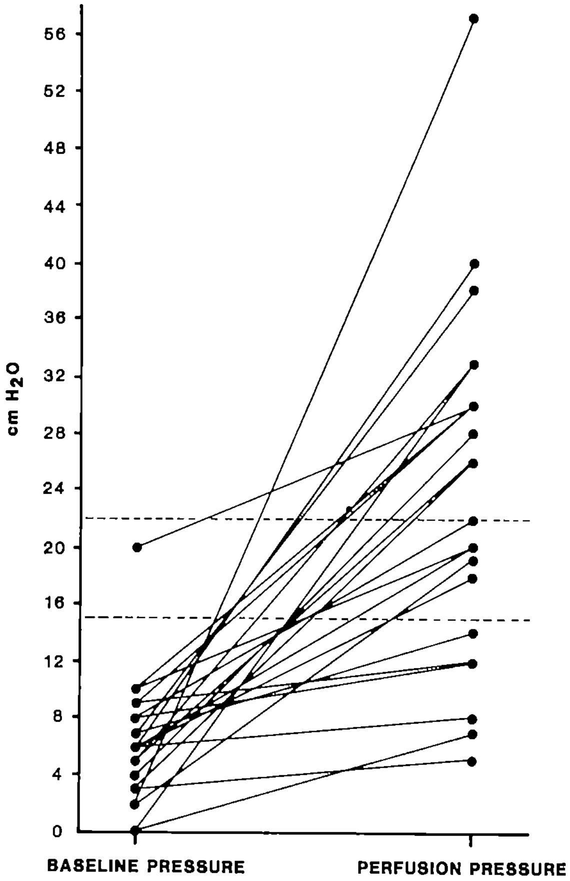

Fig. 1 Outcome of an intra-operative pressure flow study in 22 patients Baseline pressures lay between 0 and 20 cm H_2O with a majority between 2 and 10. During perfusion 6 patients showed a slight increase, 4 to 5 patients showed an equivocal response and the rest an obstructed response

There was no correlation between the outcome of the intra-operative pressure flow test and gain in function. The increase in function was most prominent in the low pressure group (Fig. 2) but numbers were too small for this to be significant.

When related to the level of function preoperatively, 6 of the 9 patients with a significant gain after 1 year had an initial pre-operative function of less than 20%.

There was no correlation between age and functional gain.

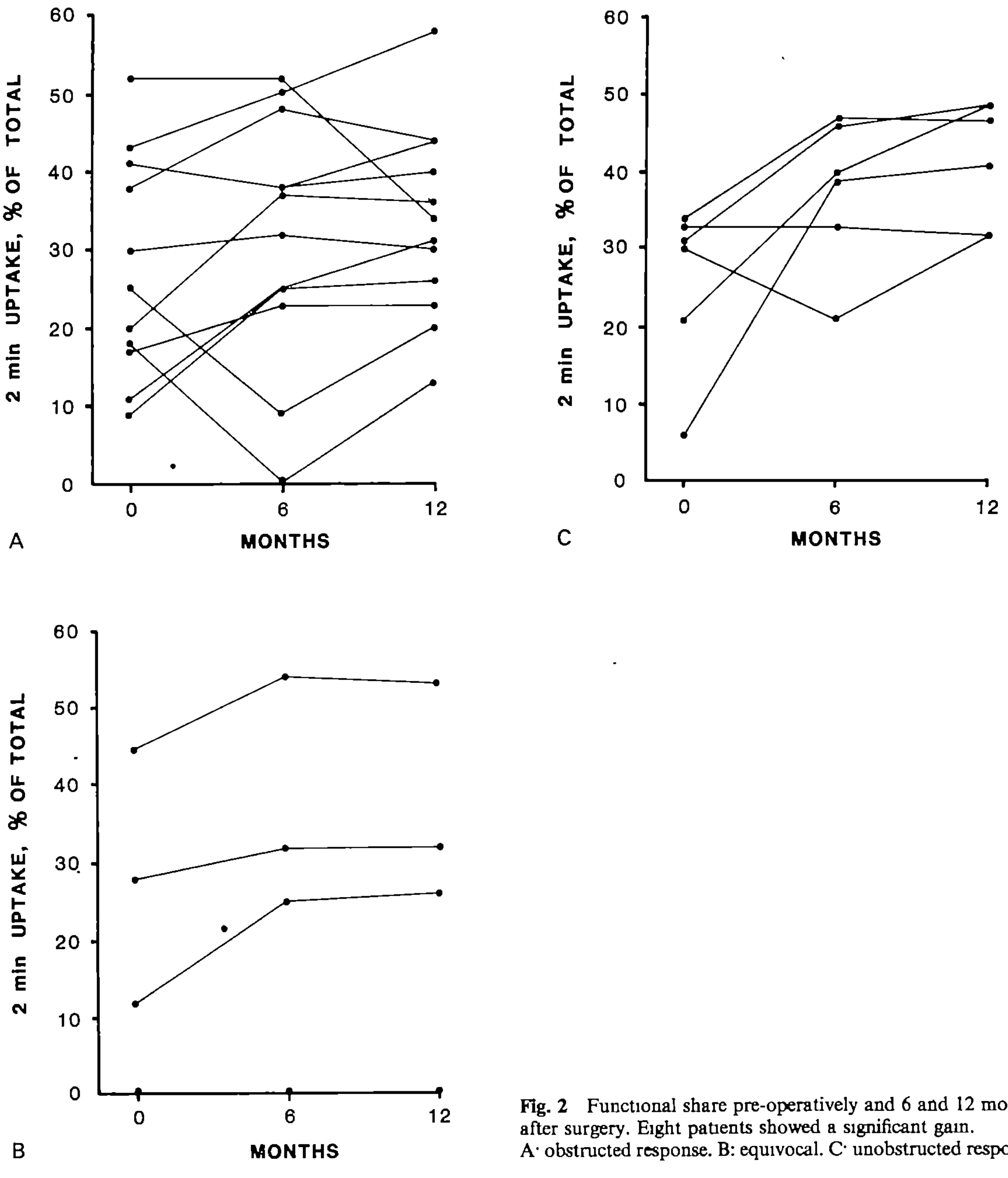

Fig. 2 Functional share pre-operatively and 6 and 12 months after surgery. Eight patients showed a significant gain.
A: obstructed response. B: equivocal. C: unobstructed response.

Discussion

The present study employed two methods in the assessment of hydronephrosis: pressure measurements to estimate transport function and renography to assess kidney function.

The pressure measurements were done intra-operatively rather than pre-operatively (Whitaker, 1979). We showed in a previous study that the pressure response to high urine output was the same both pre-operatively and per-operatively (Djurhuus, 1980), and the data obtained by pressure measurements in the present study are thus comparable with data from previous studies.

The renography measurement used in the assessment of kidney function was the 2-min isotope uptake, widely considered as representative of kidney function. Repeated pre-operative renography performed at intervals of 1 or 2 days showed consistency concerning this measurement regardless of the state of hydration (Djurhuus *et al.*, unpublished data).

This study showed a high percentage of kidneys with impaired function, when compared with our previous experience and that of others (Bratt *et al.*, 1977).

In this study almost half of the patients with impaired function pre-operatively showed a significant gain. This in accordance with our observations in a larger study (Djurhuus *et al.*, unpublished data) and the findings of Bratt *et al.* (1977). We were unable to relate this functional gain to the age of the patients, to successful surgery or to determination of the degree of obstruction prior to reconstruction.

When a patient presents with idiopathic hydronephrosis or the condition is revealed during investigation for unrelated problems, it falls into one of three categories: (1) preserved renal function combined with symptoms, (2) preserved function without symptoms, and (3) impaired function.

Categories 1 and 3 clearly contain the candidates for reconstructive surgery regardless of any pre-operative attempt to distinguish between different types of hydronephrosis. Patients in the first category undergo reconstructive surgery to relieve symptoms and those in the third category to stabilise or increase function. The second group of patients, with normal renal function and without symptoms, might be subjected to further investigation in order to demonstrate stable function or progressive disease. High-rate perfusion of the dilated area with simultaneous pressure measurements to reveal significant obstruction has a sound theoretical basis: provocation simulating high urine output can reveal a high pressure response which might damage the parenchyma of the kidney. Experiments in pigs have, however, questioned the basis of pressure flow studies, since standardised obstructions show a considerable overlap with the normal system as far as pressure responses are concerned (Mortensen *et al.*, 1984). Moreover, chronic partial obstruction in pigs seldom shows abnormal pressures during perfusion (Mortensen *et al.*, 1983).

Both the present study and previous investigations have shown that the pressure flow test, like measurements of baseline pressure and pressures during diuretic load (Djurhuus, 1980), is not a reliable measure of obstruction and the eventual outcome of surgery.

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The Authors

J C Djurhuus, MD, PhD, Associate Professor.
S. S Sørensen, MD, Registrar.
T M. Jørgensen, MD, Senior Registrar
F Taagehøj-Jensen, PhD

Requests for reprints to: J C. Djurhuus, Institute of Experimental Clinical Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

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Low Temperature and Conventional Scanning Electron Microscopy of Human Urothelium

W. G. STAFF, J. F. S. MIDDLETON, J. A. MORRIS and K. OATES

Department of Urology, Royal Lancaster Infirmary; Department of Biological Sciences, University of Lancaster; Department of Pathology, Lancaster Moor Hospital, Lancaster

Summary—The appearance of fixed dehydrated non-neoplastic human urothelium viewed by conventional scanning electron microscopy (CSEM) is different from that of frozen hydrated human urothelium viewed by low temperature scanning electron microscopy (LTSEM). In the fixed dehydrated material the surface is formed by well defined, polygonal, domed superficial urothelial cells which have prominent surface microridges. In places intermediate urothelial cells are visible and they have surface microvilli. In the frozen hydrated material viewed by LTSEM most of the surface is smooth. This is formed in part by a glutaraldehyde soluble extracellular secretion which may be a mucin barrier to bacteria. We believe that the rest of the smooth surface is formed by superficial urothelial cells which are not well defined and which lack microridges. There are islands of rounded cells lacking microvilli which are probably intermediate urothelial cells as they correspond in appearance with the intermediate urothelial cells seen in freeze fractured material.

It seems likely that fixation and dehydration will cause some change in surface configuration and in theory the frozen hydrated material should more closely resemble the natural state. We believe that LTSEM will be of value in investigating normal and diseased urothelium.

Conventional scanning electron microscopy (CSEM) has proved to be of value in the investigation of normal and diseased urothelium (Jacobs *et al.*, 1976; Kjaergaard *et al.*, 1977; Newman and Hicks, 1977; Hodges, 1979; Nelson *et al.*, 1979; Price *et al.*,1980; Davies and Hunt, 1981; Jacobs *et al.*, 1981). However, tissue for CSEM is fixed and dehydrated prior to examination and it seems likely that this will cause some change in surface configuration. Low temperature scanning electron microscopy (LTSEM) is a new technique which allows frozen hydrated tissue to be directly viewed (Echlin, 1978; Echlin *et al.*, 1978; Bullock *et al.*, 1980; Carr *et al.*, 1980; Hook *et al.*, 1980; Pawley *et al.*, 1980; Gardner *et al.*, 1981; Carr *et al.*, 1983; Oates *et al.*, 1984). This avoids the harmful effects of chemical fixation and dehydration and at least in theory the images so obtained should more closely resemble the *in vivo* appearance. A further advantage of LTSEM is that electrolytes are frozen *in situ* and the electrolyte composition of cells can be estimated using X-ray microanalysis (Hunt and Oates, 1977; Marshall, 1980; Gupta and Hall, 1981; Potts and Oates, 1983; Middleton *et al.*, 1984). There have been few morphological studies of human material using this technique and no previous study of urothelium.

We have compared the appearance of non-neoplastic human urothelium using both CSEM and LTSEM and found significant differences.

Materials and Methods

Specimens

Specimens of ureter and renal pelvis were obtained from nephrectomy specimens for renal carcinoma and at operations for pelviureteric junction reconstruction. Bladder biopsies were taken from

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patients undergoing elective surgery for prostatic hyperplasia using a conventional resectoscope, the bladders having been previously irrigated with distilled water. A total of 61 specimens from 21 patients was obtained. The first 17 paired biopsies were irrigated by 30 ml of isotonic saline for 1 min and then one of the pair was fixed in glutaraldehyde and the other promptly frozen in nitrogen slush. The subsequent 16 specimens were irrigated by saline and then frozen. A further 8 specimens were rinsed in distilled water for 1 min and then frozen. Three specimens were rinsed in saline, then fixed overnight in glutaraldehyde and subsequently frozen in nitrogen slush. In every case parallel biopsies were obtained and processed for conventional light microscopy.

Conventional Scanning Electron Microscopy

Specimens were fixed overnight in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.1, at room temperature. They were washed in several changes of buffer and post-fixed in 1% osmium tetroxide for 30 min. After a further wash, specimens were dehydrated in an alcohol series (30%, 50%, 70%, 80%, 90% and 100%, 30 min in each). They were placed in increasing concentrations of amyl acetate in ethanol until 100% amyl acetate was reached and then dried in a critical point drying apparatus using liquid carbon dioxide. Tissues were sputter coated with gold and examined at tilt angles of 0° or 20° in a JEOL JSM 50A scanning electron microscope at an accelerating voltage of 20 kV. In addition, two specimens were examined in the SEM mode in a JEOL TEMSCAN at an accelerating voltage of 40 kV.

Low Temperature Scanning Electron Microscopy

The apparatus which was developed in Lancaster, and its method of use, have been described by Gardner *et al.* (1981). However, a new development is the incorporation of a large low impedance port connecting the microscope column to the liquid nitrogen vacuum flask which is described below.

After rinsing in saline or distilled water, the specimens were adhered to specially designed stubs using conductive carbon cement and then plunged into nitrogen slush (−210°C). The specimens were subsequently stored in liquid nitrogen and when required the liquid nitrogen was made slushy by vacuum evaporation and the specimens were transferred in a low pressure atmosphere of dry nitrogen gas to the cold stage of the JEOL JSM 50A SEM. Transfer was completed within 40 s. The cold stage was maintained below −192°C by circulating liquid nitrogen. Condensation of vapours in the microscope column on to the specimen surface was minimised by three design features. The cold stage is 7°C cooler than the specimen surface and vapours will preferentially condense upon it. Furthermore, there is a separate adjustable cold plate which is also 7°C cooler than the specimen surface. In addition, the vacuum flask which holds the liquid nitrogen supply to the cold stage derives its vacuum from the microscope column via a large low impedance port. Thus the outer surface of the inner lining of the vacuum flask provides a large surface at the temperature of liquid nitrogen (−196°C) for condensation. This feature contributes to the high vacuum obtained which is better than 1×10^{-6} Torr.

Twenty-nine specimens (25 rinsed in saline and 4 rinsed in distilled water) were treated as follows. The specimens were observed uncoated at an accelerating voltage of 10 kV. Most of the specimens had surface ice, formed because the specimens were wet when frozen. The ice was removed by allowing the specimen temperature to rise slowly over 20 min to −90°C, which is above the sublimation point of water in this system but below its recrystallisation temperature. Most of the ice was removed by the time the specimen reached −90°C and the temperature was then quickly dropped to below −130°C (the sublimation point of pure water in a perfect vacuum) in under 20 s. The specimens were then placed on an airlock cold pedestal (−176°C) and coated with 25 nm of gold/palladium by high vacuum evaporation. During the coating process the specimen temperature rises by a further 20°C. The specimens were then transferred to the cold stage and examined by the secondary electron mode at an accelerating voltage of 20 kV and a beam current of 0.1 nA using tilt angles of 0° and 20°.

The three specimens which had been fixed in glutaraldehyde and then frozen in nitrogen slush were examined by LTSEM in exactly the same way as the above.

Three of the frozen specimens were fractured under liquid nitrogen using artery forceps. The fractured faces were then examined by LTSEM after coating with gold/palladium.

Three specimens, two rinsed in distilled water and one rinsed in saline, were transferred to the cold stage and then allowed to warm to −90°C. They were then kept between −95°C and −85°C for 6 h and observed uncoated at 10 kV as they slowly dehydrated in the column.

Six specimens, four rinsed in saline and two in distilled water, were frozen, transferred to the cold stage and then allowed to warm to −60°C. The specimens were observed uncoated as they dried in the column.

Results

The biopsies processed for light microscopy showed normal or hyperplastic transitional epithelium with a varying degree of inflammation in the subepithelial connective tissue. There was no evidence of epithelial dysplasia or neoplasia.

The 17 specimens of urothelium which had been fixed in glutaraldehyde were examined by CSEM. They showed features similar to those described by many workers (Kjaergaard *et al.*, 1977; Hodges, 1979; Price *et al.*, 1980; Davies and Hunt, 1981). Low power views showed that the urothelial surface contained a series of folds (Fig. 1). At higher magnifications individual cells were seen. Most of the surface was formed by superficial urothelial cells which were polygonal, flat or domed, had prominent surface microridges, clearly defined cell boundaries and occasional surface pits approximately 0.5 µm in diameter (Figs 2, 3). In places the surface layer was discontinuous, revealing underlying intermediate urothelial cells (Fig. 4) which were smaller and rounder and had numerous spherical or rod-shaped microvilli on their surfaces (Fig. 4a).

The 29 specimens of urothelium which were frozen and then examined by LTSEM after surface etching showed a quite different appearance. Low power views did show a folded urothelial surface but at higher power most of the surface was smooth (Fig. 5). There were no microridges, no microvilli and cell boundaries were indistinct. There were, however, small surface pits (Fig. 6) which may correspond to pinocytic vesicles. This smooth surface was interrupted in places by rounded cells with labyrinthine lateral processes which interdigitated with those of adjacent cells (Fig. 7). These foci probably represent intermediate cells, although we could not establish with certainty that they were at a lower level than the surrounding surface. Four of the 29 specimens had been rinsed in distilled water before freezing and the LTSEM appearance was indistinguishable from that of the other 25 specimens which had been rinsed in saline.

Three frozen specimens were fractured and the fractured faces were examined by LTSEM (Figs 8-11). The superficial cells formed a single dense layer at the luminal surface with no discernible cell boundaries. The intermediate and basal cells were smaller and had numerous cell processes which interdigitated with those of adjacent cells across prominent intercellular spaces. In places the superficial cell layer was discontinuous and the intermediate cells were exposed to the surface (Fig. 9). The morphology of the intermediate cells seen in the fractured material corresponded with the morphology of those cells which were classified as intermediate (Fig. 7) on the basis of surface views.

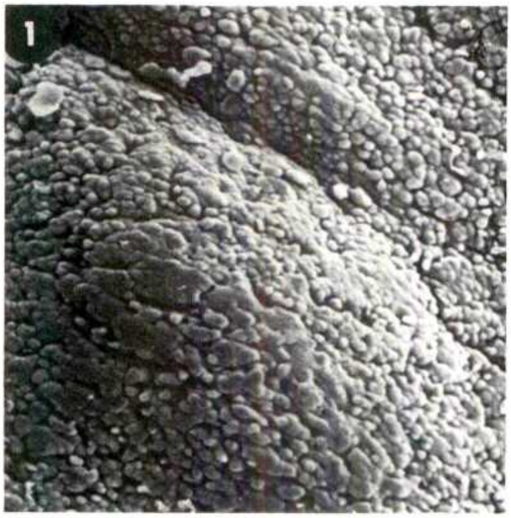
The three specimens which were fixed in glutaraldehyde, then frozen and examined by LTSEM showed clearly defined domed superficial urothelial cells (Fig. 12) and the appearance was more akin to that seen in fixed material by CSEM than in frozen material by LTSEM. However, microridges were not well developed and microvilli were not seen.

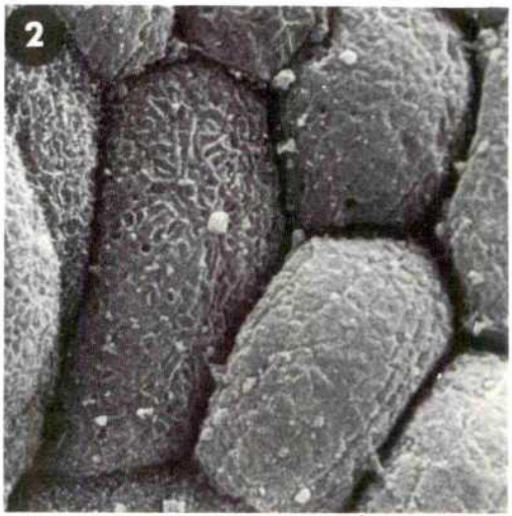
Three frozen specimens were observed uncoated at −90°C as they slowly dehydrated in the microscope column over 6 h. Surface ice had disappeared by the time the specimens reached −90°C, revealing a smooth surface. As the specimen subsequently dried the surface appearance gradually changed. Over most of the surface the rather indistinct outlines of cells became more defined (Fig. 13), but in places a thin extracellular layer cracked during drying and revealed underlying superficial cells. There was no detectable difference between the appearance of the specimen that was rinsed in distilled water and the two that were rinsed in saline before freezing.

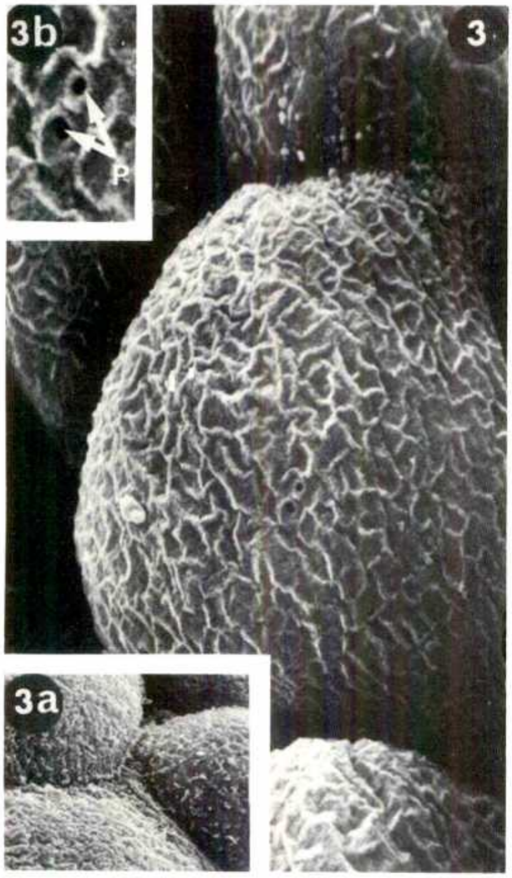
The six specimens etched at −60°C showed features similar to those of the above three. Over most of the surface, cell outlines became distinct, whilst in places an extracellular layer cracked and dried (Figs 14, 15). The more rapid drying at this temperature made the distinction between extracellular layer and the surface of superficial cells easier, but it must be appreciated that rapid sublimation can damage the surface and at −60°C ice crystals may grow in the specimen. Again the appearance of the specimens rinsed in distilled water was the same as that of those rinsed in saline.

Discussion

The surface appearance of unfixed hydrated urothelium viewed by LTSEM is quite different from that of fixed dehydrated urothelium viewed by CSEM. It seems likely that fixation and dehydration will cause some surface distortion and at least in theory the images obtained by LTSEM should







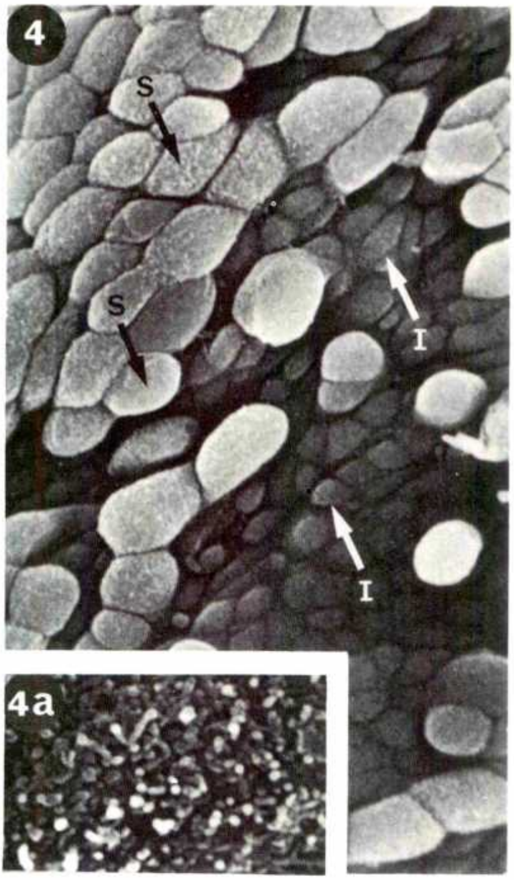
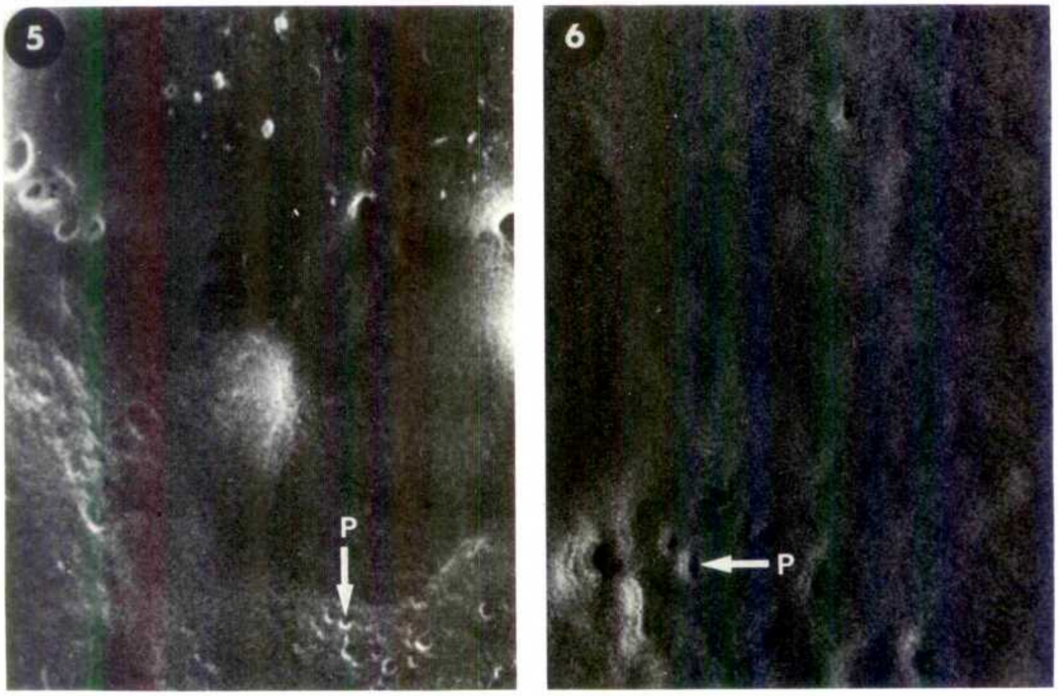


Fig. 1 Low power views show a folded surface (CSEM × 125). **Fig. 2** The superficial cells are flat or dome shaped with polygonal outlines (CSEM × 1600). **Fig. 3** The luminal membrane of superficial cells shows numerous microridges (CSEM × 3300). **Fig. 3a** Superficial cells show clearly defined cell boundaries (CSEM × 1000). **Fig. 3b** Higher magnification detail of Figure 3 shows the presence of surface pits (P, arrowed) CSEM × 6800). **Fig. 4** Superficial cells (S, arrowed) overlie smaller intermediate cells (I, arrowed) (CSEM × 600). **Fig. 4a** The intermediate cells have surface microvilli (CSEM × 6800).



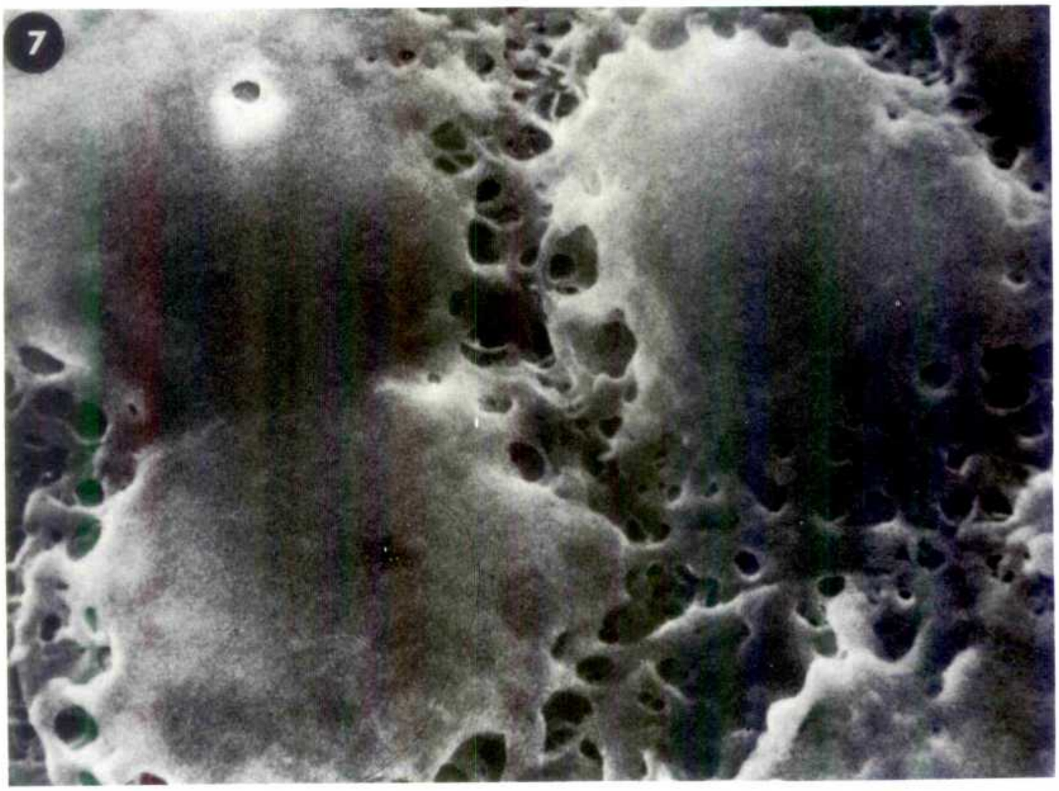
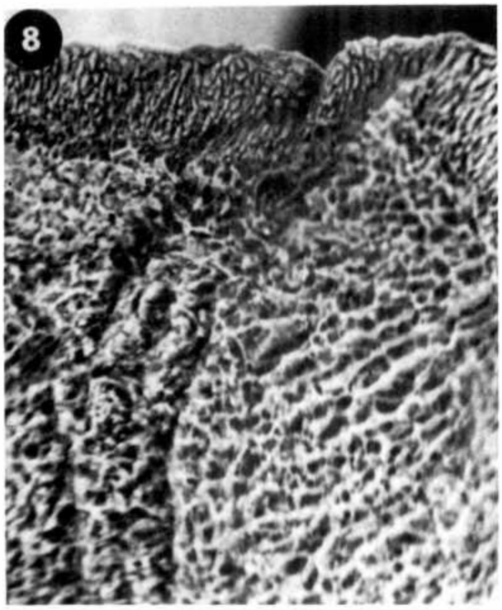
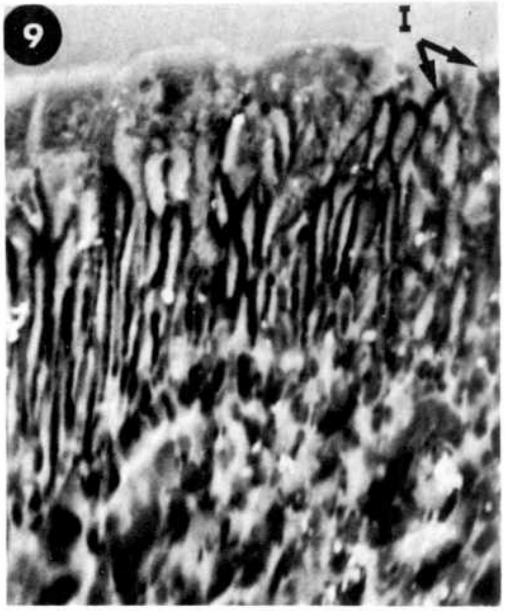
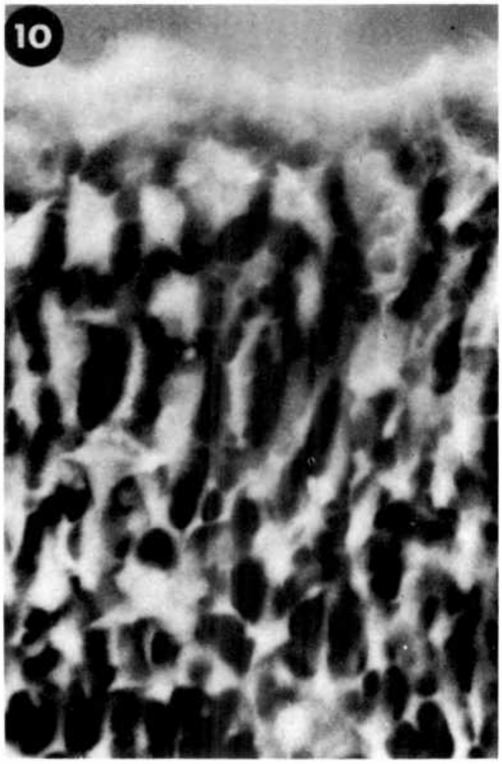


Fig. 5, 6 Superficial cells are smooth and essentially featureless, apart from small pits (P, arrowed). Microridges are absent and cell outlines are indistinct (LTSEM Fig. 5 × 1850; Fig. 6 × 11,000) (saline rinsed). **Fig. 7** Intermediate cells show no surface microvilli but numerous labyrinthine processes and intercellular spaces (LTSEM × 5000) (saline rinsed).







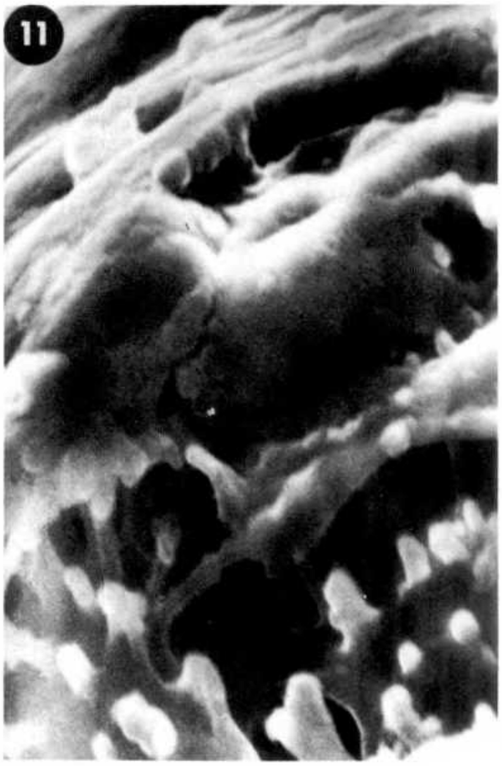
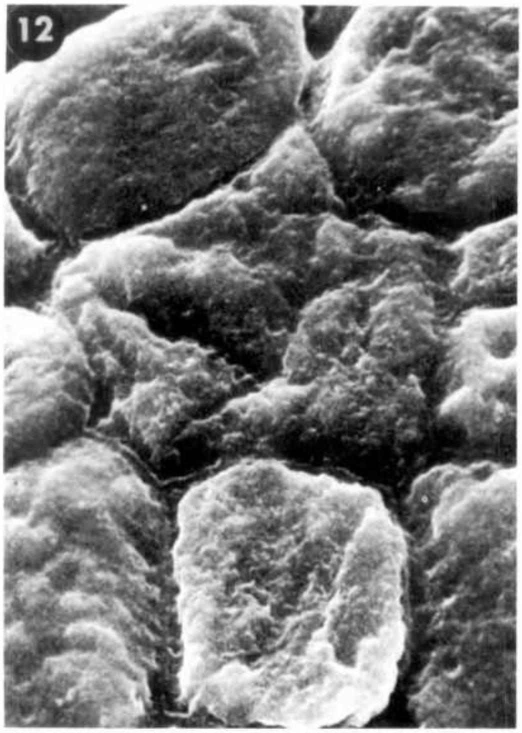
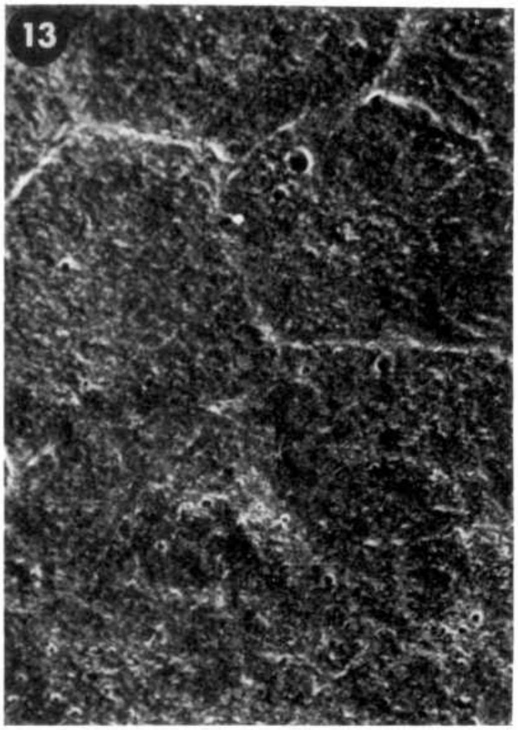
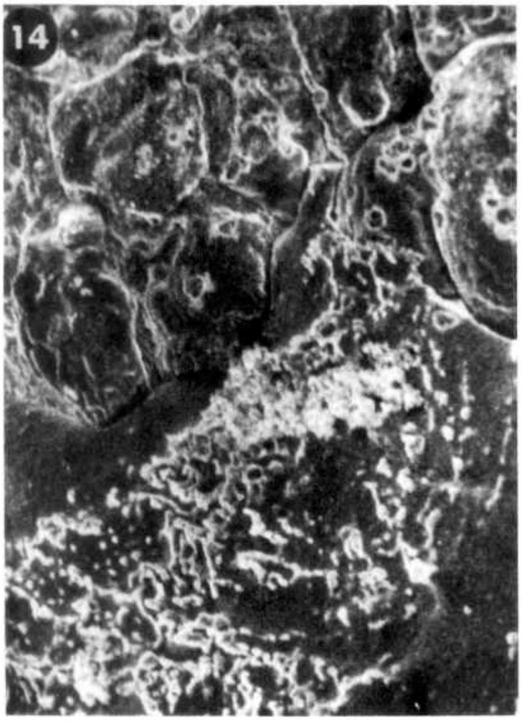


Fig. 8 Low power view of the urothelium (LTSEM, Freeze-fracture × 150). **Fig. 9, 10** Superficial cells form a dense thin layer without apparent intercellular spaces. The cells with labyrinthine processes and intercellular spaces are intermediate in position. In places (I, arrowed) intermediate cells are exposed at the surface (LTSEM, Freeze-fracture, Fig. 9 × 400; Fig. 10 × 1000). **Fig. 11** Fractured cell processes of intermediate cells resemble enlarged microvilli (LTSEM, Freeze-fracture × 3500).







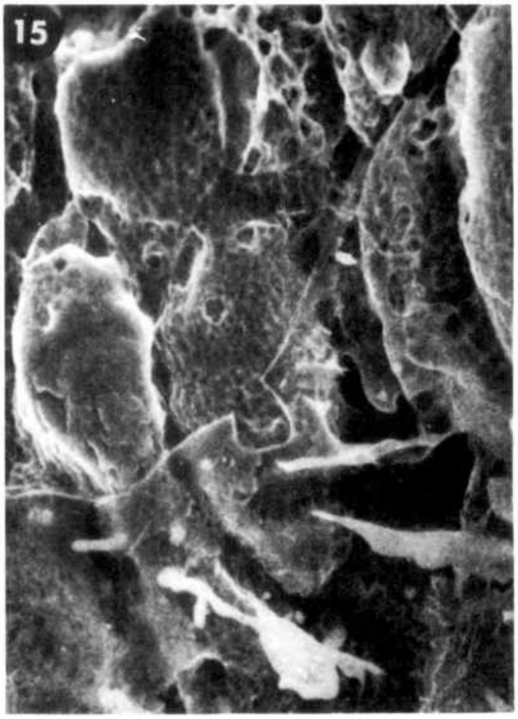


Fig. 12 Glutaraldehyde fixed frozen urothelium viewed by LTSEM. The superficial urothelial cells are clearly defined (× 1300).
Fig. 13 Frozen urothelium dried in the microscope column at −90°C. Cell outlines are now more clearly defined (LTSEM × 1300).
Fig. 14 An extracellular layer (L) is visible (LTSEM × 1050). **Fig. 15** The same field as in Figure 14 after drying in the microscope column at −60°C. The extracellular layer (L) has cracked, revealing underlying cells (LTSEM × 1050).

more closely resemble the *in vivo* appearance. However, LTSEM is a new technique and possible sources of artefact must be carefully considered. The specimens were frozen in nitrogen slush (−210°C). This gives a rapid rate of freezing and the surface 5 to 8 μm is free of detectable ice crystals (Seveus, 1978) and therefore ice crystal distortion is unlikely to affect the surface views. However, ice crystals will form deeper in the tissue and the freeze fracture images may have been modified by this occurrence. Most of the urothelial surface seen by LTSEM is smooth. This smooth surface is either formed by the surface of superficial urothelial cells or by an extracellular layer overlying the urothelial cells. If an extracellular layer is present, then this could be either a bladder secretion or some artefact of preparation. If it is an artefact of preparation, the possibilities include (i) unsublimed ice, (ii) unsublimable constituents of the isotonic saline buffer, and (iii) condensed column vapours. We do not regard any of these sources of artefact as likely. The urothelium is wet when frozen and a layer of ice will form on the surface. This can be recognised morphologically as ice charges and degrades the image. The ice can be removed by etching at −90°C and when this is done the surface is still smooth. Three specimens were etched at −90°C for 6 h and it is inconceivable that a layer of ice could still obscure the surface after this treatment (Robards and Crosby, 1979). It is unlikely that the smooth surface is formed by unsublimable constituents of the saline wash as the same appearance is obtained when the specimens are washed in distilled water. Condensation of column vapours on to the specimen surface is minimised by the 7°C temperature differential between the specimen surface and the cold stage, the provision of an adjustable cold plate, and the design of the liquid nitrogen vacuum flask which provides an additional large cold surface for condensation. Furthermore, condensation on the specimen surface has not been a problem with other material examined in this apparatus (Hunt and Oates, 1977; Carr *et al.*, 1980; Gardner *et al.*, 1981; Potts and Oates, 1983; Middleton *et al.*, 1984; Oates *et al.*, 1984). To investigate these possibilities further we fixed three specimens of urothelium in glutaraldehyde, then froze them in nitrogen slush and examined them by LTSEM. The surface was formed by clearly defined domed superficial urothelial cells (Fig. 12) somewhat similar in appearance to those seen in fixed dehydrated tissues examined by CSEM. If the smooth surface seen in the unfixed material was a consequence of the freezing technique, then the glutaraldehyde fixed material examined by LTSEM should also have been flat. The fact that it was not argues against the idea that the smooth surface is artefactual and suggests that glutaraldehyde either removes some surface secretion or alters the morphology of the superficial cells or does both. When specimens are dried in the microscope column at −90°C it becomes apparent that part of the urothelial surface is formed by a thin extracellular layer of material as it cracks and dries, revealing underlying cells (Figs 14, 15). However, over most of the surface there is a gradual definition of cell outlines (Fig. 13), although the cells never become as clearly defined as in fixed material seen by CSEM. Thus we believe that part of the smooth surface is formed by an extracellular layer which is a bladder secretion and not an artefact of the freezing technique. The rest of the surface is probably formed by the surface of superficial urothelial cells, although we cannot entirely exclude the possibility that the entire surface is covered by a thin layer of bladder secretion.

The smooth surface of the fully hydrated material was interrupted in places by rounded cells with labyrinthine lateral processes interdigitating with those of adjacent cells (Fig. 7). We suspect that these cells correspond to the intermediate cells seen by CSEM, and although they were not clearly at a different level from the surrounding surface, freeze fracture studies revealed similarities between these cells and cells which were clearly intermediate in location.

It is interesting to try to relate the known functions of urothelium to the markedly different images obtained by CSEM and LTSEM. Urothelium has a remarkable property of maintaining an impermeable barrier between urine and body fluids whilst accommodating large changes in luminal surface area as in bladder contraction and dilatation. When the bladder contracts the luminal membrane of the superficial urothelial cells could fold or membrane could be incorporated into intracytoplasmic vesicles and the surface remain flat. The images seen by CSEM are in keeping with the former mechanism, whilst the images seen by LTSEM are consistent with the latter. Morphometric studies (Minsky and Chlapowski, 1978), measurement of urothelial capacitance during stretch (Lewis and de Moura, 1982) and the observation that ferritin instilled into the lumen of the distended bladder appears in the lumen of the intracytoplasmic vesicles after bladder contraction (Porter *et al.*, 1967) provide support for the concept that intracytoplasmic vesicles are incorporated into the luminal surface during bladder dilatation and reformed from the surface during contraction. The morphometric studies by Minsky and Chlapowski (1978) also show evidence of surface folding but this is in fixed material. However, the studies of Lewis and de Moura (1982) on unfixed urothelium show a biphasic response of capacitance to stretch, indicating that some degree of urothelial surface folding may occur, although this does not necessarily imply that individual cell surfaces are folded. Thus the LTSEM images are not at variance with known urothelial function. One possible explanation for the difference between the LTSEM and CSEM images is that fixation induces contraction and the fixed cells are thereby folded. However, as cell outlines become discernible in the etched unfixed material (Fig. 13), the cells are seen to be similar in size to those in the fixed material (Figs 12, 3) and thus it appears unlikely that this is a complete explanation for the observed folding. The one surface detail noted in the otherwise smooth and featureless LTSEM images of the superficial urothelial cells were small pits (Fig. 6) which may represent a stage in the formation of intracytoplasmic vesicles from the surface membrane. If this explanation is accepted, then the observation of these pits provides further support for our view that we are visualising the superficial urothelial cells and that the surface is not entirely obscured by an extracellular excretion, but we cannot exclude the possibility that these pits are artefacts (Severs, 1980) induced by etching as the surface does become somewhat more pitted during prolonged etching (Fig. 13).

The presence of an extracellular bladder secretion is also of interest and may be of importance to concepts concerning the interaction of bacteria and urothelial cells. There is experimental evidence that the bladder secretes an acid soluble mucin layer (Parsons *et al.*, 1975, 1977) which interferes with bacterial adherence to urothelial cells, and this may correspond to the surface layer seen by LTSEM.

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The Authors

W G. Staff, MD, FRCS, Consultant Urological Surgeon, Royal Lancaster Infirmary.

J F. S Middleton, BSc, Research Assistant, Department of Biological Sciences, Lancaster University

J. A Morris, MRCPath, Consultant Pathologist, Lancaster Moor Hospital.

K Oates, PhD, Senior Research Officer, Department of Biological Sciences, Lancaster University

Requests for reprints to W G Staff, Department of Urology, Royal Lancaster Infirmary, Lancaster LA1 4RP

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Inhibition of Spontaneous Contractile Activity in Isolated Human Detrusor Muscle Strips by Vasoactive Intestinal Polypeptide

R. B. KINDER and A. R. MUNDY

Departments of Surgery and Urology, Guy's Hospital, London

Summary—In a study of 75 isolated human detrusor muscle strips, spontaneous contractions and an associated sustained rise in basal tension were observed in 43 (57%). Vasoactive intestinal polypeptide (VIP) caused significant reductions in the frequency and amplitude of spontaneous contractions and a fall in basal tension. The results suggest that VIP may have a role as an inhibitor of spontaneous activity in the human detrusor.

During a series of experiments using isolated human detrusor strips under isometric conditions it was noted that many preparations developed spontaneous contractions of variable frequency and amplitude which were usually accompanied by a rise in basal tension. Such behaviour is as yet unexplained but may be evidence of an intrinsic mechanism involved in maintaining detrusor tone *in vitro*.

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide which has been detected by immunocytochemistry and radioimmunoassay in many parts of the central and peripheral nervous systems, including the nerves of the urinary bladder (Gu *et al.*, 1983). In view of this and since VIP is known to cause smooth muscle relaxation (Fahrenkrug and Emson, 1982), the effect of VIP on the spontaneous activity of human detrusor *in vitro* was studied.

Materials and Methods

Specimens were taken from the dome of the bladder at open operation from a group of patients with a variety of urodynamic abnormalities and from patients with urodynamically normal bladders (Table 1). The specimens were stored in Krebs solution (composition mM: NaCl 118, KCl 4.7, $MgSO_4$, $7H_2O$ 1.18, $NaHCO_3$ 25, K_2PO_4 1.03, $CaCl_2$ 2.5, glucose 11.1) at 4°C for 1 to 24 h (mean 17.5 h). Strips of detrusor measuring 5 × 1 × 1 mm were suspended in a 1-ml jacketed organ bath in Krebs solution maintained at a temperature of 37°C and bubbled with a 95%O_2, 5%CO_2 mixture. The preparation was stretched initially to a tension of 5 g and subsequent changes were recorded isometrically using a Grass FT03 force-displacement transducer and a Devices M4 recorder. A period of 90 min was allowed for equilibration, during which time the bath fluid was changed every 20 min.

Table 1 Development of Spontaneous Contractions in Isolated Human Detrusor Strips

Type of bladder	*No. of strips*	*Spontaneous contractions* (%)	*No. tested with VIP*
Normal (adult)	29	13 (45)	7
Child (ureteric reflux)	8	3 (38)	1
Defunctioned	6	1 (17)	0
Interstitial cystitis	10	0	0
Neuropathic	11	8 (73)	5
Unstable	11	6 (55)	3
Total	75	31 (100)	16

The strips showing spontaneous contractile activity that was sustained for at least 1 h after

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equilibration of the specimen were treated with VIP in final bath concentrations of 10^{-7}M and 10^{-6}M. Any change in activity was recorded until a steady response had been achieved. The VIP was then removed by several changes of bath fluid and the muscle was observed for signs of recovery.

Results

All of the detrusor strips showed a spontaneous reduction in basal tension from 5 to 1.0 to 1.5 g during the first 20 to 30 min. Of 75 strips studied, 43 (57%) developed spontaneous contractions of variable frequency and amplitude within the 90 minutes' equilibration period and this was accompanied by a simultaneous rise in basal tension to about 2.0 to 3.0 g (Fig. 1). There was no evidence of an adverse effect on the development of spontaneous activity as a result of storage at 4°C. Six (37.5%) of the 16 specimens studied within 4 h of removal developed contractions compared with 28 (47.5%) of the 59 stored for 18 to 24 h. Similarly, there was no difference in either the frequency or amplitude of the contractions or in the basal tension in relation to the duration of storage prior to study.

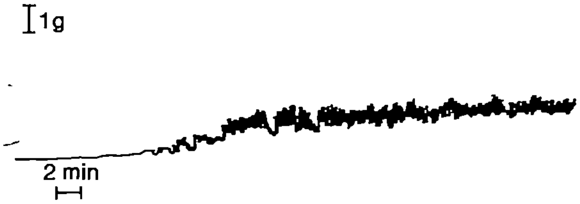

Fig. 1 Development of spontaneous contractions with a rise in basal tension

Tetrodotoxin failed to inhibit any aspect of spontaneous activity in bath concentrations of up to 10^{-5}, which suggests an intrinsic mechanism which is not nerve-mediated.

In 12 preparations contractions ceased before the end of the equilibration period, whilst in 31 they were maintained for part or all of the subsequent experiment. Sixteen of the 31 preparations exhibiting sustained spontaneous activity were tested with VIP at concentrations of 10^{-7}M (Fig. 2) and 10^{-6}M (Fig. 3). Both concentrations caused a significant reduction in amplitude, frequency and basal tension (Table 2). The maximum effect was reached 2 min after addition of the VIP and lasted for 8 to 10 min, after which muscular activity was again noted (Fig. 4).

Specimens from neuropathic and unstable bladders showed a greater tendency to develop spontaneous activity (Table 1). They also tended to show contractions of greater amplitude and higher frequency, with a higher basal tension and a greater sensitivity to VIP, but these differences failed to reach statistical significance.

Discussion

Spontaneous contractile activity of detrusor muscle strips *in vitro* has been demonstrated in several mammalian species including man (Andersson *et al.*, 1977, Cowan and Daniel, 1983) and is related to the length and applied tension of the preparation (Finkbeiner and Bissada, 1980). In the present study 57% of the preparations developed

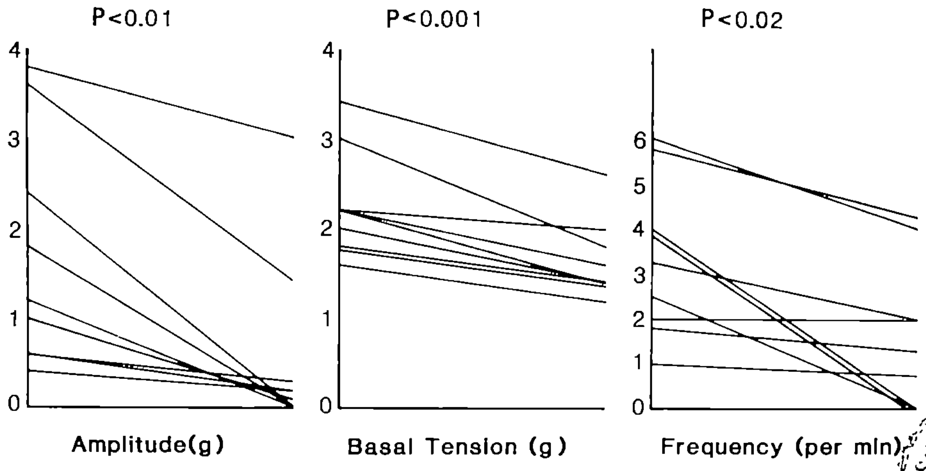

Fig. 2 Inhibition of spontaneous contractions and basal tension by VIP 10^{-7}M (n=9).

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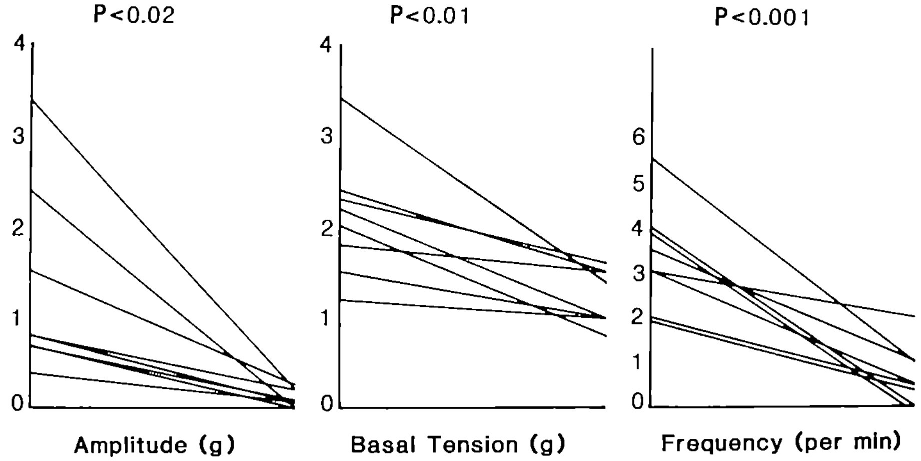

Fig. 3 Inhibition of spontaneous contractions and basal tension by VIP 10^{-6}M (n=8)

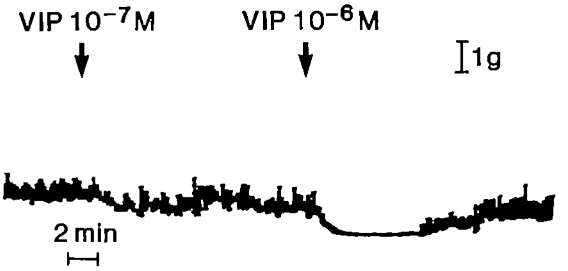

Fig. 4 Inhibition of spontaneous contractions and basal tension by VIP in bath concentrations of 10^{-7}M and 10^{-6}M

spontaneous contractions which were unaffected by tetrodotoxin and were thus presumably not nerve-mediated. While the significance of this aspect of detrusor behaviour *in vitro* is not clear, it appeared that tissue from neuropathic and unstable bladders had a greater tendency to exhibit such contractions.

VIP causes relaxation of vascular and non-vascular smooth muscle of several types (Fahrenkrug and Emson, 1982) and has been found to inhibit the spontaneous activity of uterine smooth muscle (Ottesen *et al.*, 1981). It is therefore reasonable that it should also inhibit spontaneous activity in the smooth muscle of the human urinary tract. In this respect VIP-containing nerves have been shown to be present in human detrusor; furthermore, such nerves are present in reduced numbers and with a reduced concentration of VIP in the unstable bladder (Gu *et al.*, 1983), a finding which is consistent with its pharmacological action.

As spontaneous activity is related to applied tension and as this study shows a marked reduction of spontaneous activity by VIP, it can be postulated that VIP might act *in vivo* to reduce the tension and spontaneous activity of the detrusor induced by stretching of the bladder wall as it fills. It would then follow that a disturbance of this mechanism might be relevant to the urodynamic dysfunction seen in the unstable and neuropathic bladder.

Table 2 Reduction of Spontaneous Contractions and Basal Tension by VIP 10^{-7}M and 10^{-6}M

	VIP concentration	*Before VIP*		*After VIP*	
		Range	*Mean*	*Range*	*Mean*
Amplitude (g)	10^{-7}	0.4-3.8	1.7	0-3.0	0.6*
	10^{-6}	0.7-3.4	1.3	0-0.3	0.1**
Basal tension (g)	10^{-7}	1.6-3.4	2.2	1.2-2.6	1.6†
	10^{-6}	1.2-3.4	2.1	0.8-1.6	1.2*
Frequency (per min)	10^{-7}	1.0-5.8	3.4	0-4.3	1.7**
	10^{-6}	2.0-5.5	3.4	0-2.0	0.7†

* $P<0.01$, ** $P<0.02$; † $P<0.001$ when compared with pre-treatment values

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This study forms part of work to be submitted as a thesis by R. B. Kinder for the Degree of Master of Surgery of the University of London.

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The Authors

R. B. Kinder, FRCS, Lecturer in Surgery.

A. R. Mundy, MS, FRCS, MRCP, Senior Lecturer in Urology and Consultant Urological Surgeon.

Requests for reprints to: A. R. Mundy, Department of Surgery, Guy's Hospital, St Thomas Street, London SE1 9RT.

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Female Chronic Urinary Retention

A. M. DEANE and P. H. L. WORTH

Institute of Urology, London

Summary—Thirty-seven cases of female chronic retention are reviewed. Only 13 patients had neurological disease. The problems encountered in diagnosis and management are presented.

Painless retention of urine, with a residual volume exceeding the normal capacity, constitutes chronic retention. It is associated with frequent voiding, overflow incontinence and recurrent infection, but upper tract obstruction in the female is rare as detrusor pressure is usually low. The condition merits little attention in traditional textbooks and published series are few. Fox *et al.* (1976) described 14 idiopathic cases and suggested that there was a predominant psychogenic element, allowing progressively excessive bladder distension—a modesty type of bladder. Secondary bladder neck changes, perhaps from infection, were also blamed, requiring bladder neck resection to re-establish voiding. Acute retention of urine is a more common finding in the female and often has gynaecological or urological causes (Doran and Roberts, 1976).

Bladder neck obstruction was once thought to be a common condition in the female and resection of the bladder neck was commonly practised (Emmett *et al.*, 1950). The increasing use of urodynamic measurements has shown that true bladder neck obstruction in the female is very rare (Farrar *et al.*, 1976). It is now recognised that chronic retention in the female is usually due to detrusor failure: the bladder neck cannot be expected to open in the absence of detrusor activity unless it is incompetent. Procedures to weaken the bladder neck may have to be considered to restore voiding in detrusor failure.

Patients and Methods

Thirty-seven patients were referred over a 5-year period. Their ages ranged from 18 to 77 years (mean 48). There was a variety of symptoms, especially overflow incontinence, recurrent infections and abdominal distension. Several patients reported infrequent voiding—as little as once a day—prior to retention.

All patients underwent a full history and examination including neurological as well as video urodynamics (Bates *et al.*, 1970). No patient had significant upper tract deterioration. Urodynamic findings were those of detrusor failure with no detrusor activity on voiding. End filling pressure did not exceed 30 cm of water. Sensation on filling was often intact, but this was difficult to interpret. Careful note was made of the presence or absence of bladder neck competence. Reflux was unusual, suggesting neurological disease.

Several patients, especially those in the younger age group, were referred for a neurological opinion. This invariably led to a myelogram but no patient was found to have a lesion amenable to surgery. This may be due to referral patterns, however. The possibility of a central disc protrusion should be remembered in these patients (Emmett *et al.*, 1968) but is unlikely in the presence of normal perineal sensation and bulbocavernosus reflex. We now include the eliciting of sacral evoked responses (Rockswold and Bradley, 1977). If these are absent a myelogram is required.

Neurological disease was present in 13 cases (Table 1), multiple sclerosis being the most common diagnosis. Two patients who had undergone rectal excision were included, although mechanical

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

Table 1 Neurological Chronic Retention (13 Patients)

Multiple sclerosis	7
Diabetes mellitus	2
Post-rectal excision	2
B_{12} deficiency	1
Spina bifida	1

causes (perineal prolapse of the bladder) may contribute as well as neurological damage.

Twenty-four patients with no overt neurological disease were included. No patient was defined as obstructed, all having detrusor failure without evidence of outlet obstruction. Possible aetiological factors are listed in Table 2. The incidence of hysterectomy may be no greater than in a control group of similar age and doubts have been cast (Mundy, 1982) on whether hysterectomy does cause neural damage to the bladder. Repair procedures may produce an obstructive element or may highlight an underlying detrusor failure. Psychological causes are often quoted as a potent factor in female retention (Barrett, 1978). Two patients were diagnosed by psychiatrists as hysterical; one was wheelchair-bound. Several patients received antidepressants or anxiolytics for minor psychiatric illness. One patient with chronic retention (excluded from this series) reverted to normal voiding after stopping the tricyclic antidepressant Prothiaden.

Table 2 Idiopathic Detrusor Failure (24 Patients). Possible Aetiological Factors

Anxiety or depressive illness	11
Hysteria	2
Prior hysterectomy	5
Suprapubic repair	3
Vaginal repair	2

Treatment and Results

Patients were initially taught to perform intermittent clean self-catheterisation and most were able to perform this adequately. There was a high rate of patient resistance and several either stopped or requested alternative treatment. Some patients would not even contemplate self-catheterisation, which created suspicions of psychological overlay.

Drugs were frequently prescribed but were almost universally unhelpful. Three of the neuropathic patients did respond (2 to distigmine bromide and 1 to phenoxybenzamine). Two of the idiopathic patients responded to subcutaneous bethanechol but this was not used as a long-term therapy.

Procedures to lower outlet resistance were tried in most cases (Table 3). Otis urethrotomy was tried first, at which time a suprapubic catheter was often inserted to supervise voiding attempts and residual urine. The Otis was expanded until it would no longer move easily in the urethra (calibration), expanded a further 10F and a cut performed at 12 o'clock. If this was unhelpful and the bladder neck was incompetent at cystography a further over-dilatation to around 55F was performed with Hegars dilators. When the bladder neck was competent, a cautious bladder neck incision was performed at 12 o'clock using direct vision and a urethroplasty speculum. Few fibres were cut at first and we were willing to repeat the procedure. Cystography is useful in revealing whether the required minor degree of bladder neck incompetence has been reached.

Table 3 Procedures to Lower Outlet Resistance

Otis urethrotomy/ over-dilatation	19 cases 8/19 satisfactory voiding
Bladder neck incision	13 cases 6/13 satisfactory voiding

Forty-four per cent of patients reverted to satisfactory voiding after lowering of outlet resistance. One patient who complained of stress incontinence after a bladder neck incision (her voiding was unchanged) underwent bladder neck repair and returned to self-catheterisation. There were no other complications from these procedures. Five patients were diverted on a long-term basis, two by suprapubic catheter, combined with urethral closure in one case, and three by ileal loop diversion. Twelve patients were happy to remain on self-catheterisation, while six remained in some degree of chronic retention.

Discussion

Chronic retention in the female is almost invariably accompanied by detrusor failure but absence of outlet resistance co-ordination must also play a part. Many females are able to void satisfactorily without any evidence of detrusor activity on voiding cystography and the strain void in the female is normal (Abrams *et al.*, 1983). It is easy to see that neurogenic dysfunction could prevent pelvic floor relaxation but why this should occur in the idiopathic cases is less clear. Bladder biopsies from this group (Kirby *et al.*, 1983) have failed to show any muscle degeneration, denervation or any abnormality on clinical testing of autonomic function.

The easiest course when considering management is to insist on intermittent clean self-catheterisation and not to offer any other procedure. Many patients will accept this but others will go elsewhere for help. Procedures to lower outlet resistance, especially bladder neck incision, undoubtedly have a risk of producing stress incontinence, but this must be kept in perspective. Delaere *et al.* (1983) found stress incontinence in only 2 of 32 females after bladder neck incision (6.25%). Both of these were after repeated incisions. They reported benefit from the procedure in 56% of cases.

Chronic retention in the female is a diagnostic and therapeutic challenge. While self-catheterisation is a satisfactory form of management, approximately 40% can be returned to normal voiding by urethrotomy, over-dilatation or bladder neck incision. The risks of stress incontinence may have been over-emphasised.

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The Authors

A. M. Deane, FRCS, Urological Registrar, Norfolk & Norwich Hospital, Norwich.

P. H. L. Worth, FRCS, Consultant Urologist, Institute of Urology.

Requests for reprints to: A. M. Deane, Department of Urology, Norfolk & Norwich Hospital, Brunswick Road, Norwich, Norfolk NR1 3SR.

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Treatment of the Neuropathic Bladder by Enterocystoplasty and Selective Sphincterotomy or Sphincter Ablation and Replacement

T. P. STEPHENSON and A. R. MUNDY

Departments of Urology, Cardiff Royal Infirmary; Departments of Surgery and Urology, Guy's Hospital, London

Summary—Sixty-one patients with lower urinary tract neuropathy were treated surgically, either to achieve continence or to prevent or arrest renal deterioration, or both. Most were myelodysplastics and all but two were ambulatory. Three techniques were employed, depending on the detrusor/sphincter behaviour and the sex of the patient: enterocystoplasty alone, with or without selective sphincterotomy and/or intermittent self-catheterisation; total sphincter ablation and an artificial sphincter; or, most commonly, enterocystoplasty combined with sphincter ablation and an artificial sphincter. Continence was achieved in 58 patients, though nocturnal enuresis was sometimes a problem; renal deterioration was arrested in 13 of 14 patients and renal function remained stable in all of the other patients.

The treatment of the neuropathic bladder has undergone fundamental changes over the past decade, especially in children (Mundy *et al.*, 1982; Rickwood *et al.*, 1982). In children with myelomeningocele the changes have resulted from a number of factors. Amniocentesis has reduced the number of such children being born. A selective policy in most centres offering surgical treatment only to those with the smaller or closed lesions has reduced the number of children with major deformities (Lorber and Salfield, 1981) but has led to an increasing number in whom a neuropathic bladder is their main or only handicap (this group forms the bulk of this series). The results of lower urinary tract diversion are so disappointing in the longer term (Schwarz and Jeffs, 1975; Elder *et al.*, 1979) that this method of treatment is now virtually never used for the control of congenital neuropathic incontinence or renal impairment. Indeed many such patients have been "undiverted" (Frank *et al.*, 1982; Stone *et al.*, 1982) and although this series includes a small number of previously diverted patients, most are primary reconstructions, since the patients suitable for undiversion had already been reconstructed.

Patients and Methods

Sixty-one patients, 59 of whom were ambulatory, have been reconstructed, either to arrest further renal deterioration or to achieve continence, or both; 13 had been previously diverted.

A preponderance of patients had congenital myelodysplasia (Table 1) and this was reflected by the fact that two-thirds were under 20 when operated upon (Fig. 1). Nevertheless, several

Table 1 Aetiology

Myelodysplasia	36
Spinal trauma	7
Unexplained	6
Transverse myelitis	4
Multiple sclerosis	2
Central disc lesion	2
Isolated autonomic neuropathy	2
Spinal tumour	1
Sacral agenesis	1

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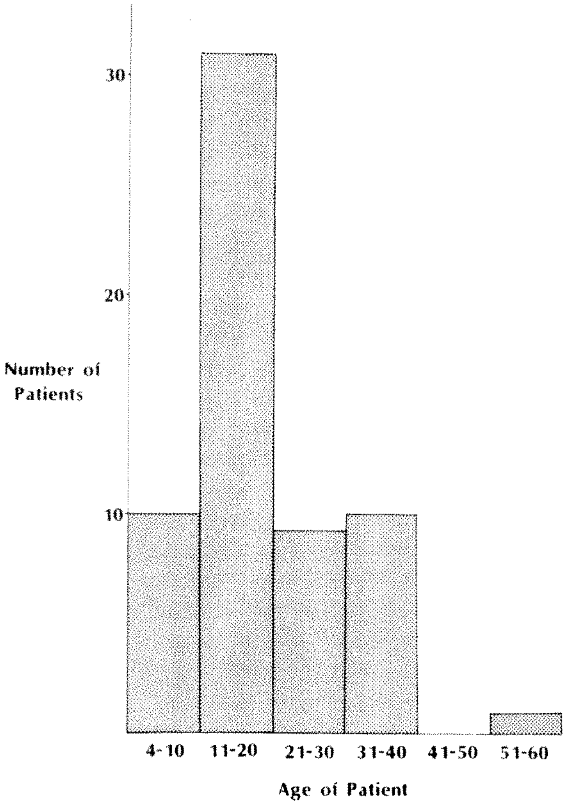

Fig. 1 Age distribution.

patients with congenital lesions presented in their twenties and thirties—for example one male presented in his late thirties with a urethral erosion, having controlled his incontinence with a Cunningham clamp for 30 years.

In 17 patients, deteriorating renal function was the prime indication for surgery. In three, all with cutaneous ureterostomy diversions, end stage renal failure had been reached and reconstruction was planned with transplantation in mind. All had detrusor/sphincter dyssynergia, but it was clear that the really ominous prognostic signs were very poor compliance early in filling (Fig. 2) or high pressure phasic contractions with reflux (Fig. 3), and if these were seen even in the presence of normal upper tracts, they were considered an absolute indication for intervention.

Patients were divided into three groups: those who had a cystoplasty but no sphincter (17); those who had an artificial sphincter but no cystoplasty (18)—all of these patients had acontractile bladders and required a per-operative or previous sphincterotomy; finally, the largest group, who required both a cystoplasty, sphincterotomy and an artificial sphincter to achieve a low pressure system and continence without outflow obstruction (26).

In the majority (44), substitution ileocaecocystoplasty was the technique used. If significant ureteric "failure" was present, this method was considered mandatory, and tunnelling or nippling

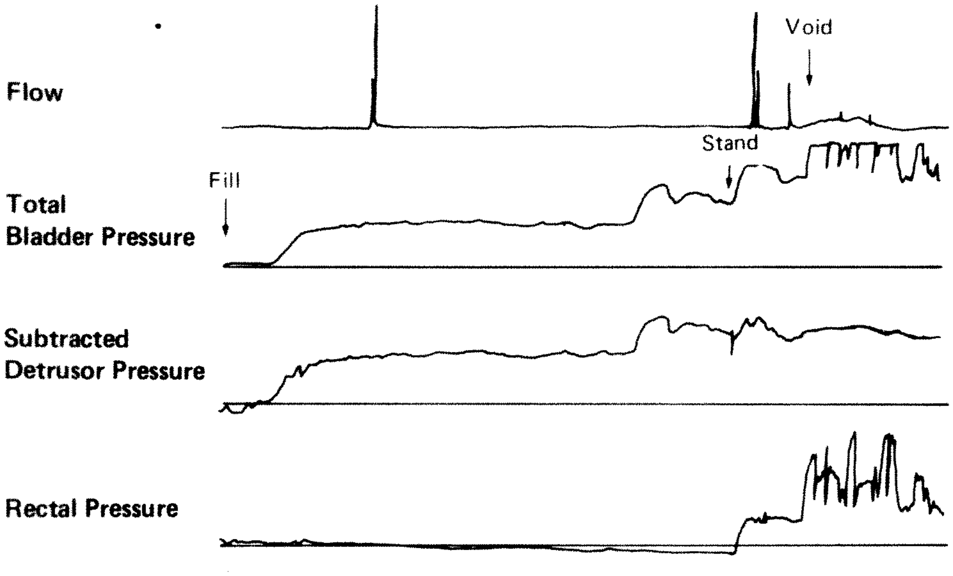

Fig. 2 Cystometry shows poor compliance early in filling.

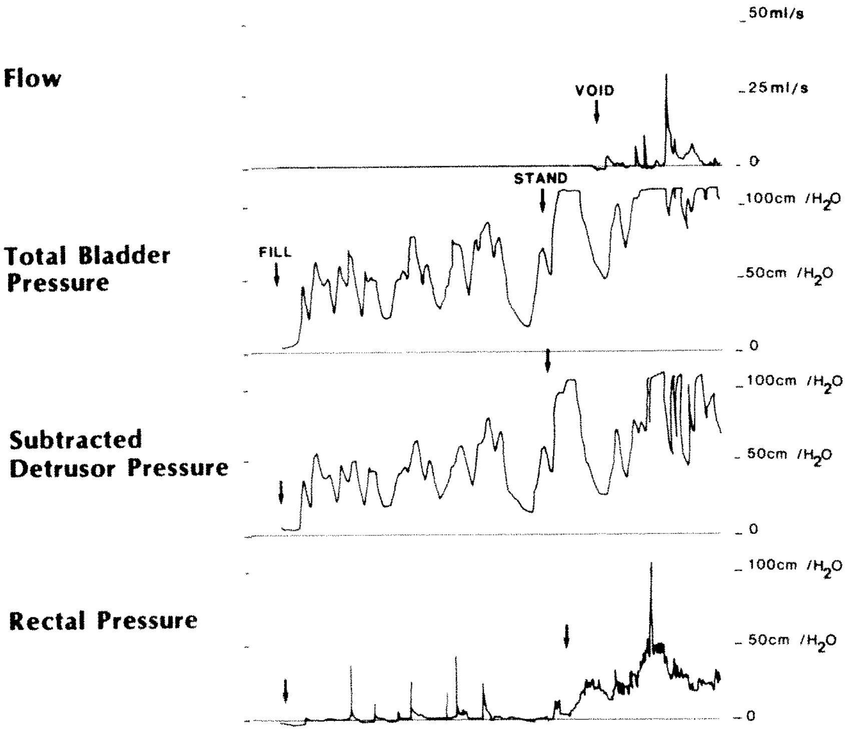

Fig. 3 Cystometry shows high pressure phasic contractions.

of the ureters was avoided because of the high risk of obstruction with acontractile ureters (Stephenson and Jeffs, 1984). In 5 patients, an "opened" sigmoid segment was used after subtotal cystectomy, and in 5 a small bowel "clam" procedure was done (Bramble, 1982).

In the Cardiff series the ureters were always reimplanted, usually by split cuff nipples into the ileal tail of the ileocaeco-cystoplasty. In the Guy's series the ureters were usually but not always reimplanted, and routinely in all patients with reflux or deteriorating renal function or who had had previous surgery.

The technique of ileocaeco-cystoplasty is not generally difficult, but certain surgical requirements in the neuropathic lower urinary tract are mandatory. Except in the "clam" procedure, subtotal cystectomy is essential, leaving just a cuff of bladder for placement of the sphincter cuff or, if bladder sensation is present, the trigone is also left to preserve the perception of fullness of the reconstructed unit. A large segment of caecum and ascending colon is required, longer than would be used for reconstruction in, for example, patients with interstitial cystitis or the contracted tuberculous bladder, and this may be made technically easier by swinging the segment on the right colic vessles. The use of an omental wrap aids healing of the anastomosis of the caecum to the trigone or bladder neck and is probably an insurance against infection, especially where a sphincter cuff has been placed at the time of the cystoplasty. Meticulous attention to surgical technique has kept complications of such major reconstruction to a minimum, both in the short and longer term.

Where an artificial sphincter was required, a bladder neck cuff was preferred. This site was always chosen where a cystoplasty was not required, and was routinely performed at the time of the cystoplasty when required, in the Guy's series. In the latter the sphincter was usually primarily activated, though primary deactivation was the rule in Cardiff (Mundy and Stephenson, 1984).

Two non-ambulatory myelodysplastic patients were reconstructed, one because of the inability to maintain a penile condom, and the other (with bilateral ureterostomies) because of inability to maintain a stomal appliance. The latter was reconstructed using the ileocaecal segment and a subcutaneous sphincter cuff.

Results

Overall diurnal and nocturnal continence was achieved in 55 patients and diurnal continence in a further three. Nine patients had significant nocturnal enuresis due to phasic contractions of their cystoplasties (Fig. 4), but six of these were controlled by Lomotil in doses up to 10 mg nocte, having failed to respond to conventional therapy. Some required laxative therapy concurrently. Of the 14 patients with deteriorating renal function, one who presented with a creatinine of 500 mmol/l has reached end stage renal failure. The remaining 13 patients have stable renal function, in some at creatinine levels higher than pre-operatively, presumably because of reabsorption from their bowel reconstruction, but with improved or stable upper tracts. The three patients who presented with end stage renal failure and have been transplanted are also stable, with normal renal function.

Many of the patients required one or more associated surgical procedures to achieve the end result (Table 2) and there was a significant complication rate (Table 3), requiring further surgical intervention in 12 patients. However, only 2 patients have been "abandoned"—one (non-ambulatory) myelodysplastic who was unable to work his sphincter and one girl with a hyperactive cystoplasty unresponsive to Lomotil who has been rediverted.

Table 2 Associated procedures other than enterocystoplasty

Artificial urinary sphincter	44
Sphincterotomy	31
Undiversion	13
Selective sphincterotomy	4
Renal transplant	3
Urethroplasty	2
Bladder neck incision	2
Phenolisation	2
Colposuspension	1

Table 3 Complications

Enuresis	10	6 controlled by Lomotil 1 rediverted
Revision of artificial sphincter	6	
Major surgical complications	4	perivesical abscesses cutaneous fistula bowel obstruction (2)
Renal failure	1	

Group I—Cystoplasty but no sphincter (17)

Ten patients (all female) are continent and on intermittent self-catheterisation. The other seven are continent and voiding. Four males required selective sphincterotomy to achieve satisfactory bladder

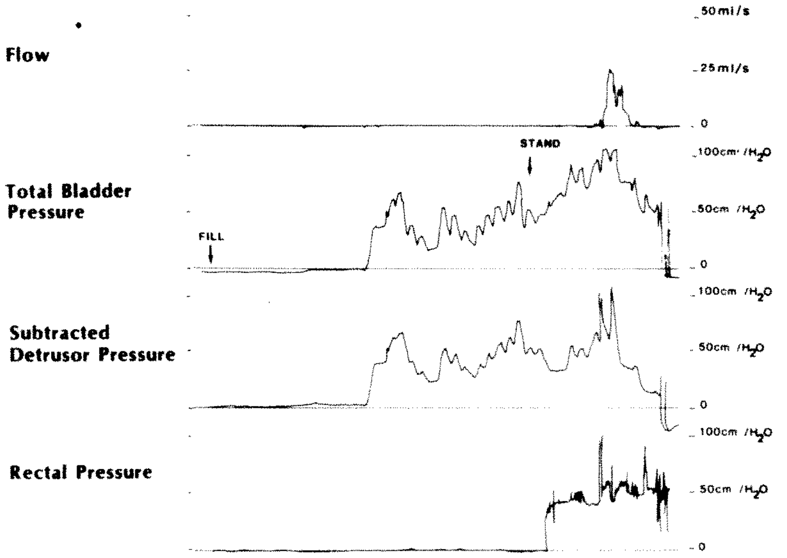

Fig. 4 Cystometry shows phasic contractions in 9 patients with significant nocturnal enuresis.

emptying. Two patients in this group have persistent nocturnal enuresis.

Group II—Sphincter but no Cystoplasty (18)

All but one (the non-ambulatory myelodysplastic) are continent. All required sphincterotomy, which was usually performed 2 weeks before sphincter implantation. In the girls, sphincterotomy was preferred to an anterior bladder flap since it requires less surgery and is equally effective.

Group III—Cystoplasty and sphincter (26)

All of these patients had detrusor sphincter dyssynergia and either poor compliance or hyperreflexia and therefore required cystoplasty, sphincterotomy and a sphincter, usually at the bladder neck. One patient has reached end stage renal failure and is awaiting transplantation and one has been rediverted (*vide supra*). One girl (with a transplant) is continent with a deactivated sphincter cuff and catheterises herself, and the boy with the subcutaneous cuff and erosion of the sphincter tubing is awaiting a further sphincter. One patient has persistent nocturnal enuresis.

Discussion

Since being ambulatory was considered an absolute requirement for reconstruction except in the exceptional circumstance of a reconstruction on to the abdominal wall, the group of patients suitable for such major reconstruction represents a relatively small percentage of the overall number of patients with congenital or acquired neuropathic lesions. In those with deteriorating renal function, arrest of further impairment could (at least in the males) be achieved by sphincterotomy alone. However, with the success rate of the current models of the Brantley-Scott artificial sphincter, this is very much a second best alternative. Similarly, in patients in whom the lower urinary tract is the main or only lesion, life-long incontinence is no longer acceptable. The age at which reconstruction should be undertaken depends partly on the surgeon's philosophy, partly on the status of the upper tracts, and partly on the problems of controlling incontinence (thus females are generally reconstructed earlier).

However, it is clearly preferable to achieve continence as soon as possible, for the child's psyche and ability to attend conventional schools, even if, for example, revision of their sphincter may be required at a later date. Even in patients with severe renal impairment with proteinuria, reconstruction is desirable, and this is borne out by the success of the small number of transplanted patients. The success rate of this combined series has been high and there have been no deaths. The main long-term problem of nocturnal enuresis has been mostly controlled by the use of Lomotil.

Very careful follow-up of these patients is required and some patients with sphincters will undoubtedly require revision in the future. However, in this group of patients continence and stable renal function must now be considered a mandatory aim with the surgical techniques currently available.

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The Authors

T. P. Stephenson, FRCS, Consultant Urologist, Cardiff Royal Infirmary.

A. R. Mundy, FRCS, Senior Lecturer in Urology and Consultant Urological Surgeon, Guy's Hospital, London.

Requests for reprints to: T. P. Stephenson, Department of Urology, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ.

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Invasive Potential of Superficial Bladder Cancer

A Study of the Relative Merits of Predictive Parameters

G. DAS, N. J. C. BUXTON and R. W. GLASHAN

Departments of Urology and Pathology, Royal Infirmary, Huddersfield

Summary—The indirect immunoperoxidase test to detect urothelial cell surface blood group antigens was performed in an attempt to assess the loss of these antigens as a prognostic predictor. In our technique A, B and O(H) blood group specific monoclonal antibodies were used. It was possible to perform the test satisfactorily on histological material from 55 cases which were superficial on presentation; 15 subsequently became invasive. The loss of surface antigens correlated well with histological grade—44.4% of G1, 87.2% of G2 and 94.1% of G3 tumours were antigen-negative.

The blood group phenotype of 114 patients was studied. In the group that subsequently became invasive, 14 of 26 (54%) were of blood group A phenotype compared with 37 of 88 (42%) in the non-invasive category.

Acetylation studies were performed on 47 cases. In the group that subsequently became invasive, 5 of 10 (50%) had the slow phenotype of the enzyme N-acetyltransferase compared with 13 of 37 (35%) in the group that remained superficial.

The primary treatment of patients presenting with superficial transitional cell carcinoma of the bladder initially gives excellent results. However, there is a recurrence rate of 50 to 70% and, in time, at least 10% will develop tumours which invade the muscle of the bladder (Greene *et al.*, 1973), with a deterioration in prognosis. Early identification of this important group could lead to more aggressive treatment at the outset.

The normal urothelium has the same blood group antigen substance on its surface as does the individual's own red cells. Loss of these surface blood group isoantigens (BGI) are said to occur in those tumours of the urothelium which generally carry a poor prognosis (Decenzo *et al.*, 1975; Lange *et al.*, 1978; Limas *et al.*, 1979; Young *et al.*, 1979). Catalona (1981) has extensively reviewed the subject. The immunological test to detect BGI has, in most series, been the Specific Red Cell Adherence Test (SRCAT), which involves adherence of indicator erythrocytes to a tissue section. The SRCA Test is technically difficult to perform and to interpret. Various authors have differed in their definition of positive reaction (*i.e.* BGI retention), as some consider adherence of erythrocytes to 30% of tumour section as positive (Coon and Weinstein, 1981; D'Elia *et al.*, 1982), while others accept a positive reaction only when more than 50% of the tumour section displayed erythrocyte adherence (Lange *et al.*, 1978; Young *et al.*, 1979). Obviously this complicates comparison of results from different centres. Moreover, conventional polyclonal blood-typing sera were used for the SRCA Test with their inherent disadvantage of batch to batch variation. Finan *et al.* (1982) reported the use of mouse monoclonal antibodies (McAbs) to human blood group isoantigens A and B in the indirect immunoperoxidase test which is considered to be superior to the SRCA Test to detect cell surface BGI (Coon and Weinstein, 1981).

Blood group phenotyping and N-acetyltransferase status have also been studied as

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possible prognostic factors in bladder cancer. Cartwright *et al.* (1983) reported an excess of blood group A phenotypes in patients with superficial transitional cell carcinoma and suggested that it was this phenotype which was most likely to proceed to invasion. Cartwright *et al.* (1982) also found that individuals with the slow sub-type of the liver enzyme N-acetyltransferase, which acetylates and thereby detoxicates carcinogenic amines, were more likely to develop bladder cancer.

The present study was designed to apply the indirect immunoperoxidase test using blood group specific monoclonal antibodies to detect loss of cell surface antigens as a prognostic index in superficial bladder cancer. In addition to McAbs anti-A and anti-B we have used anti-H for blood group O cases. We have also studied blood group phenotyping and acetylator status as other possible prognosticators.

Patients and Methods

Retrospectively from the records of the Urology Department a group of patients was identified who presented with superficial bladder cancer. All had been followed for at least 4 years and either remained superficial or at some point had progressed to invasive disease. Histological material from 55 patients was subjected to the indirect immunoperoxidase test; 114 were blood group phenotyped and 47 underwent acetylation studies.

Indirect immunoperoxidase test

Histological material Paraffin blocks were retrieved from the histopathology bank and 4 micrometer sections cut. We have also used fresh frozen material for a prospective study where the tissue was snap frozen in liquid nitrogen (−70°C) at the time of resection and subsequently 5 micrometer cryostat sections were cut.

Immunological reagents McAbs anti-A, anti-B and anti-H (A and B-cell Tech and H-Dako) were used as primary antibodies. Normal rabbit serum (Dako) in a dilution of 1 in 10 in Tris buffered saline was used to block non-specific antigen sites. Peroxidase-conjugated anti-mouse rabbit IgG (Miles-Yeda) diluted 1 in 50 in Tris buffered saline was used as the second antibody layer. Freshly prepared diaminobenzidine (DAB) was used to visualise the antigen-antibody complex as a brown precipitate (Fig.).

Indirect immunoperoxidase technique Tissue sections were mounted on glass slides, dewaxed, incubated with the primary blood group specific monoclonal antibody followed by incubation with peroxidase-conjugated anti-mouse rabbit IgG. The final reaction was produced by adding freshly prepared DAB, counter-stained with Mayer's haemalum, blued in Scott's tap water substitute, dehydrated, cleared and mounted with DPX.

Controls Strict controls were adhered to in our technique. The specificity of the McAbs was confirmed by testing against isologous and non-isologous red cells. With each test slide, a control slide was used which was incubated with an inappropriate antibody, the rest of the procedure remaining unaltered. Moreover, built-in internal controls were present in the test slide. These consisted of: (i) erythrocytes, (ii) vascular endothelium, and (iii) normal bladder epithelium (when included in the section). All of these possess the appropriate blood group isoantigen on their respective surfaces and always stain positive if the immunoperoxidase test is correctly performed. If the internal controls in the test slide were negative or the control slide showed positive staining, that particular test was considered invalid. In our series, no false positives, *i.e.* staining in the control slide, were identified.

Blood group phenotyping

The blood groups of 114 patients were obtained from the case notes and where this was unavailable, a simple blood group test was performed.

Acetylation studies

These were performed by determination of the ratio of monoacetyl dapsone/dapsone (MADDS/DDS). Each patient was given a single 50 mg tablet of dapsone orally and a blood sample taken 2 to 6 h later. Plasma was separated, stored at −20°C and sent off in batches to the Department of Clinical Pharmacology at Guy's Hospital, London, where quantitative high performance thin layer chromatography was performed to obtain plasma MADDS and DDS levels.

Results

For the indirect immunoperoxidase test to detect loss of BGI, we studied histological material from 55 cases; 15 of these subsequently became invasive, while 40 remained superficial. (The average time interval for development of invasion was 4.7 years, while the average follow-up in the second group was 7 years). Twelve of 15 (80%) initial tumours in

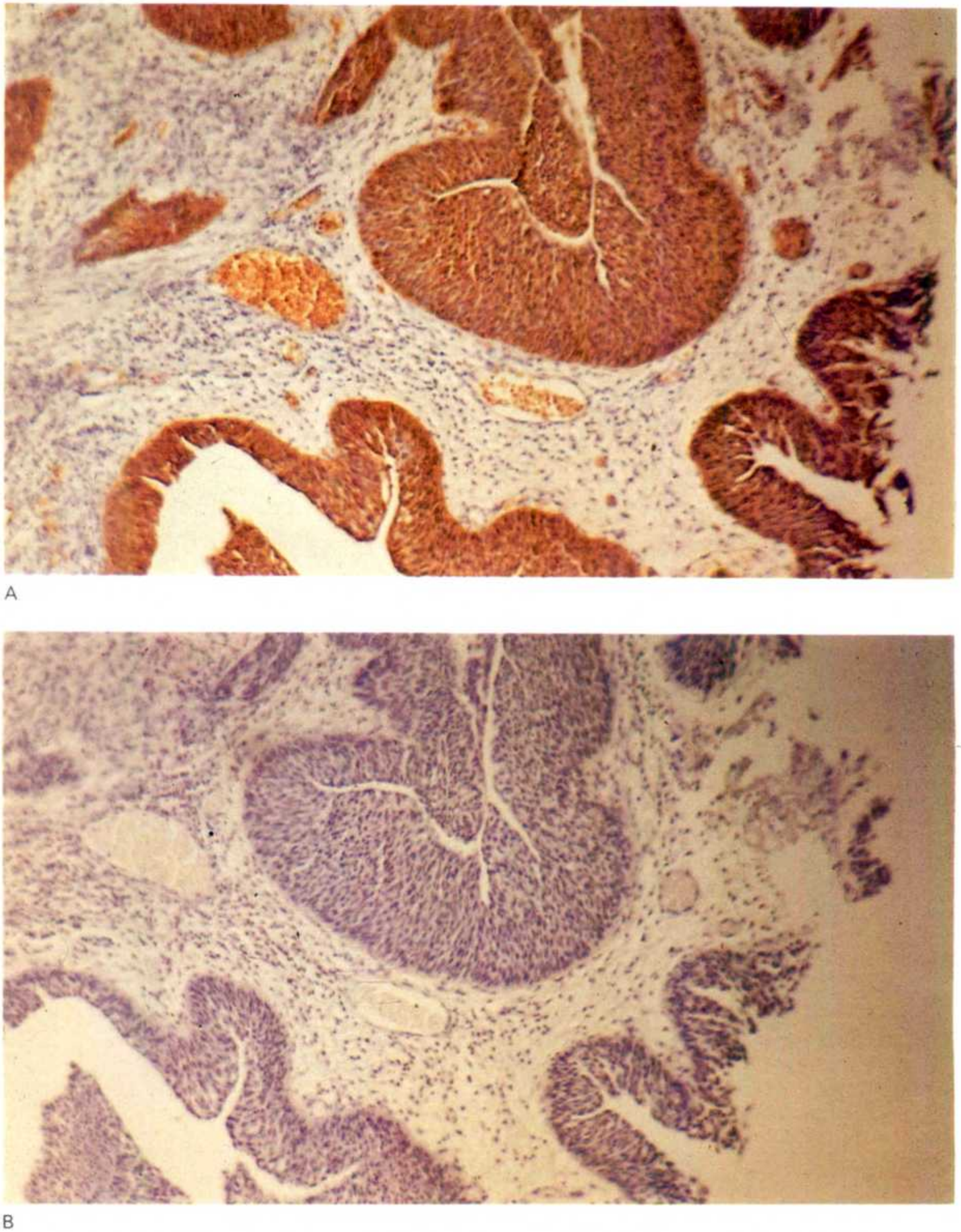

Fig. Paraffin section of transitional cell tumour. [Indirect immunoperoxidase technique (× 150)]. (A) Positive result with appropriate blood group antibody demonstrating antigen in tumour and internal controls. (B) Negative control using inappropriate antibody.

the group which subsequently became invasive showed loss of BGI, compared with 30 of 40 (75%) initial tumours which remained superficial (Table 1). A Chi-squared test comparing negatives with non-negatives in the two groups was not significant at one degree of freedom. We also studied BGI expression in a number of recurrent tumours in both groups. A total of 86 superficial tumours was studied—18 were G1, 47 G2, 17 G3 and 4 a mixture of G1 and 2. Table 2 correlates BGI expression with histological grading. Statistically, when BGI loss was compared in low grade (G1) and high grade (G2 and G3) tumours, a highly significant difference was obtained at one degree of freedom ($P<0.001$). In addition, 10 invasive tumours were studied, all of which showed loss of surface antigen.

It was possible to study blood group phenotyping in 114 cases; 26 of these developed invasive recurrences while 88 remained superficial. Fourteen of the 26 cases (54%) which became invasive were of blood group A phenotype compared with 37 of 88 cases (42%) that stayed superficial. A Chi-squared test was performed comparing blood group A versus other blood groups in the two categories. The computed value was 1.13 for one degree of freedom, which is not a significant difference. Acetylation studies were performed on 47 cases. In the invasive group 5 of 10 (50%) had the slow sub-type of the enzyme N-acetyltransferase compared with 13 of 37 (38%) in the other group. The computed value of the Chi-squared test comparing slow acetylators with others was 0.74 for one degree of freedom. This was not a significant difference.

Table 1 Results of Indirect Immunoperoxidase Test to Detect Loss of BGI

	Initial tumours (total—55)	*BGI −ve initial tumours*
Superficial → invasive	15	12 (80%)
Superficial → superficial	40	30 (75%)

Table 2 Correlation of BGI Status with Histological Grade (86 Tumours)

	BGI retained (+ve)	*BGI lost (−ve)*
G1	10 (55.6%)	8 (44.4%)
G2	5 (10.6%)	41 (87.2%)
G3	1 (5.9%)	16 (94.1%)
Total	16	65

Five tumours (4 G1 + 2 and 1 G2) showed a mixed picture.

Discussion

In our study there was no significant difference in the percentage of BGI negative initial tumours in the two categories. The presence of a large number of BGI negative initial tumours in the group that remained superficial is surprising, but may be due to selection of a large number of high grade tumours. Histological grading correlated very well with BGI expression. Consequently, the presence of a large number of high grade tumours resulted in the finding of a disproportionately large number of BGI negative tumours in this group. It is also possible that in the course of time more of these BGI negative tumours will proceed to muscle invasion. It is important to note that in this category, of the 8 BGI positive initial tumours, 5 (62.5%) had no recurrences. This benign pattern is in contrast to that found in the BGI negative tumours of this group, the majority of which had numerous recurrences and usually required vigorous follow-up treatment.

The important finding in this study is the correlation obtained between BGI expression of superficial transitional cell carcinomas and histological grading (Table 2). Forty-four point four per cent of G1, 87.2% of G2 and 94.1% of G3 tumours were found to be BGI negative, demonstrating a direct relationship between higher histological grade and loss of BGI. Statistically, this was found to be highly significant. Similar results were reported by Emmot *et al.* (1979). In four tumours of mixed grade, we found the G1 element retained BGI while the G2 element showed loss of BGI. These findings indicate the potential value of detecting loss of BGI as an index of malignant cell de-differentiation. This may well find relevance in treatment modalities which rely on tumour cell anaplasia for their effectiveness. We believe that the indirect immunoperoxidase technique using blood group specific monoclonal antibodies is a sensitive, reliable and reproducible test. A positive reaction, *i.e.* retention of BGI, is unambiguous and false negatives are ruled out by the presence of positive internal controls. Similarly, false positives are excluded by the control slide. In our study, tests on a number of specimens were invalidated (*i.e.* internal controls negative). These were mostly old blood group O tissue blocks, but also included some of blood groups A and B. We think this is due to older fixation procedures which caused denaturation of the ABH glycoproteins and glycolipids.

In blood group phenotyping, more blood group A phenotypes were noted in the group that developed invasive disease, but this did not reach statistical significance. Similarly, more slow acetylators were found in this group; again this did not reach statistical significance.

Acknowledgements

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The Authors

G. Das, MS, FRCSE, Research Fellow in Urology.
N. J. C. Buxton, MRCPath.
R. W. Glashan, FRCSE, FRCS(Glas), FRCS, Consultant Urologist.

Requests for reprints to: R. W. Glashan, Department of Urology, The Royal Infirmary, Huddersfield HD3 3EA.

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Intravesical Mitomycin C Therapy for Superficial Bladder Cancer. Report of a Multicentre Phase II Study

J. R. MacFARLANE, D. A. TOLLEY and the SCOTTISH UROLOGICAL ONCOLOGY GROUP*

Department of Urology, Royal Infirmary, Edinburgh

Summary—Twenty-five patients with early transitional cell carcinoma of the bladder (Tis Ta T1) received intravesical instillations of 40 mg mitomycin C in 40 ml water weekly for 7 weeks. The overall response rate was 70% (complete response 40%). In patients with Ta tumours the response rate was 86%. Minor toxic side effects occurred in four patients and only one patient was unable to complete the course of treatment because of side effects.

Tumours of the urothelium account for about 30% of all malignancies (UICC, 1979). Two-thirds of patients have Ta or T1 tumours when first seen but 70% will recur after complete resection and 10 to 20% of recurrences will progress to a higher grade (Gilbert *et al.*, 1978; Heney *et al.*, 1982; Lutzeyer *et al.*, 1982). The 5-year survival rate for Ta lesions is 90% but this falls to 40% for patients with T1 tumours (Pocock *et al.*, 1982). Thus careful endoscopic surveillance is necessary and any treatment which will reduce the recurrence rate and allow for less frequent cystoscopies will be welcomed by patient and surgeon.

Superficial bladder tumours are readily accessible to the action of anti-cancer drugs when instilled into the bladder and intravesical chemotherapy was first used in 1961 by Jones and Swinney in an attempt to reduce the recurrence rate in patients with superficial bladder cancer. Since then, intravesical agents have been used both for primary treatment in patients with multiple tumours and also as prophylactic therapy. Many agents have been tried in these roles and one of the most effective appears to be mitomycin C, a naturally occurring anti-tumour antibiotic derived from *Streptomyces caespistosus*. It derives its anti-tumour activity by interacting with DNA by cross-linking and inhibiting replication. The use of this agent in the treatment of superficial bladder cancer is largely confined to studies in the USA and Japan (Mishina *et al.*, 1975; Soloway *et al.*, 1981), and experience with the drug in the United Kingdom is limited to a pilot study reported by Harrison *et al.* (1983).

The purpose of this study was to assess the anti-tumour activity of mitomycin C in a dose appropriate to use in a busy urological department.

Patients and Methods

Twenty-five patients entered a co-operative multicentre study carried out by the Scottish Urological Oncology Group (SUOG). All patients had primary or recurrent multifocal transitional cell carcinoma of the bladder (Tis Ta or T1 NX MO) which could no longer be readily controlled endoscopically. All gave informed verbal consent to inclusion in the study.

The size and number of lesions seen at cystoscopy were recorded in diagrammatic form before treatment and a representative biopsy of the tumour(s) was taken in addition to random mucosal biopsies close to and distant from the tumour(s) before commencing therapy. Areas of

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* Participants in this study: T. B. Hargreave, Western General Hospital, Edinburgh; D. Kirk, Royal Infirmary, Glasgow; R. F. Deane, Western General Infirmary, Glasgow.

abnormal mucosa were also biopsied. Patients then received 7 weekly instillations of 40 mg mitomycin C dissolved in 40 ml sterile water via a urethral catheter. The catheter was removed and the solution retained in the bladder for 2 h. All instillations were carried out on an out-patient basis. Estimation of haemoglobin, white cell count and platelets was carried out on entry to the study and at weekly intervals. Blood urea, creatinine and electrolytes were estimated at monthly intervals. Symptoms relating to chemical cystitis were recorded and patients were questioned about the appearance of a skin rash. In the event of chemical cystitis occurring, mitomycin C was diluted by a further 50%.

Cystoscopic assessment was carried out 4, 8 and 12 weeks after the initial treatment and on each occasion the size, number and site of tumours were recorded. Biopsy of any remaining tumours was carried out at the 12-week cystoscopy and was combined with endoscopic destruction of the lesions.

Response was assessed according to the following criteria:

Complete response (CR)—complete disappearance of all visible disease.
Partial response (PR)—50% or more decrease in the tumour mass observed on two occasions at cystoscopy not less than 4 weeks apart.
No change.
Progressive disease—greater than 25% increase in the size of one or more measurable lesions or the appearance of a new lesion.

Results

Drug-related toxicity was observed in four patients. Three developed symptomatic chemical cystitis but all were able to complete the course of treatment after receiving a reduced concentration of the drug. One patient developed a skin eruption which was sufficiently severe to warrant his withdrawal from the study. No myelosuppression was observed. One patient died from myocardial infarction 1 week after commencing treatment.

The response rate in all cases was 70% (CR 43%, PR 27%). There was a higher response rate in patients with Ta tumours than in those with T1 tumours (Table 1). One patient with a pTa lesion was shown to have progressed to pT1 at the 12-week biopsy. In one patient a pT1 tumour progressed but there was no change in tumour stage or grade.

Table 1 Pathological Stage *vs.* Response to Mitomycin C

Stage	*Number of patients*	*Complete response*	*Partial response*	*No change*	*Progression*
pTa	14	9	3	1	1
pT1	5	—	2	2	1
pTis	1	1	—	—	—
pT1 + pTis	3	—	1	2	—
Total	23	10	6	5	2

Two patients not evaluable.

An early indication of response (sloughing of the tumour with surrounding erythema) was usually seen at the 4-week cystoscopy. Most patients were shown to have a complete or partial response by 8 weeks and only one patient had a late response at 12 weeks (Fig.).

The relationship between grade of tumour and degree of response is shown in Table 2. There was

Table 2 Histological Grade *vs.* Response to Mitomycin C

Grade	*Number of patients*	*Complete response*	*Partial response*	*No reponse*	*Progression*
G1	9	5	3	—	1
G2	13	4	4	4	1
G3	1	—	—	1	—
Total	23	9	7	5	2

Two patients not evaluable.

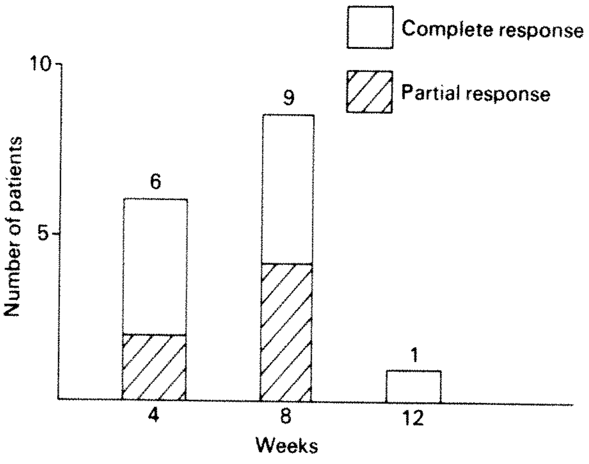

Fig. Timing of response to mitomycin C.

no significant difference in response between different grades. Severe dysplasia was present in the random biopsies in four patients, three of whom had a complete response and one a partial response. Response did not appear to be dependent on tumour size, number or site.

Discussion

This study confirms the high anti-tumour activity of mitomycin C observed by Soloway *et al.* (1981) and Bracken (1982). The overall response rate is considerably lower than that observed by Harrison *et al.* (1983), who treated a similar group of patients. However, mitomycin C was given as thrice-weekly instillations in their study and the incidence of toxic side effects was greater and was severe enough in five patients to prevent them from receiving a full course of treatment.

It is unlikely that there is significant absorption of mitomycin C from the bladder (Soloway *et al.*, 1981; Fluchter *et al.*, 1982). The occurrence of a widespread rash over the upper trunk and neck in one patient in our study instead of the more usual contact dermatitis is suggestive of drug absorption. Chemical cystitis was not a problem in our series and indicates that large doses of the drug, which is more effective when given in a high concentration, is quite safe.

The response of T1 tumours to mitomycin C therapy has been disappointing in this series and our experience contrasts with that of Harrison *et al.* (1983), who observed a 66% complete response rate. This suggests that a more intensive regime offers the best chance of response in patients with T1 disease.

Of interest is the early response of tumours to treatment by mitomycin C and it appears that, in the absence of an early response, prolonged treatment in the hope of gaining tumour control is unjustified.

This study has shown that weekly instillations of mitomycin C (40 mg in 40 ml water) are an effective, safe treatment for patients with Ta bladder cancer, but those with T1 tumours may benefit from a more intensive regime. Further studies of the drug are required to assess the optimal duration of instillations and its role as adjuvant therapy.

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The Authors

J R. Macfarlane, FRCSE, formerly Senior Urological Registrar, Royal Infirmary, Edinburgh Now Consultant Urological Surgeon, Victoria Hospital, Kirkcaldy.

D. A Tolley, FRCS, FRCSE, Consultant Urological Surgeon, Royal Infirmary, Edinburgh

Requests for reprints to· D. A. Tolley, Department of Urology, Royal Infirmary, Edinburgh EH3 9YW.

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Invasive Bladder Cancer Treated by Radical External Radiotherapy

M. O. CORCORAN, D. M. THOMAS, A. LIM, R. J. BERRY and E. J. G. MILROY

Departments of Urology and Oncology, Middlesex Hospital, London

Summary—Fifty-three consecutive, unselected patients with invasive bladder cancer, Stage T2 to T3, treated by radical radiotherapy have been reviewed. Cystectomy was reserved for patients with significant worsening of disease during treatment, histologically confirmed persistent or recurrent invasive tumour after treatment, or patients with intolerable symptoms due to radiation cystitis. In 64% of our patients a favourable tumour response to radiotherapy was seen, while a further 31% showed disease progression either during or on completion of radiotherapy. Cystectomy was performed on 22% of patients, mainly for radiation cystitis, and was not associated with a significant operative mortality rate. The crude 5-year survival rate was 42%. We conclude that radical radiotherapy is as effective as other forms of treatment for invasive bladder cancer, but that there remains a need to identify those bladder tumours destined to respond poorly to radiotherapy at an earlier stage.

Recent evidence suggests that in the management of invasive bladder cancer radical radiotherapy may be as effective as radiotherapy and cystectomy, thus avoiding the trauma, risks and detriment to quality of life which follow cystectomy (Blandy *et al.*, 1980). In addition it has been suggested that cystectomy after radical radiotherapy may be less hazardous than was thought previously (Osborn *et al.*, 1982). For the past 7 years it has been our policy to treat all patients with invasive bladder cancer primarily with radical radiotherapy, and we now report on 53 consecutive patients with invasive bladder tumour, Stage T2 to T3, treated in this manner, with a mean follow-up of 3 years.

Patients and Methods

In the period 1977 to 1982, 301 new patients with bladder cancer were diagnosed and subsequently managed at the Middlesex Hospital. Of these, 53 (17.6%) were shown to have invasive bladder tumours Stage T2 to T3. There were 36 males and 17 females with a mean age of 67.5 years (Fig. 1).

All patients were evaluated by cystoscopy, bimanual examination and endoscopic resection and deep biopsy under general anaesthesia. Histological evidence of muscle invasion was obtained

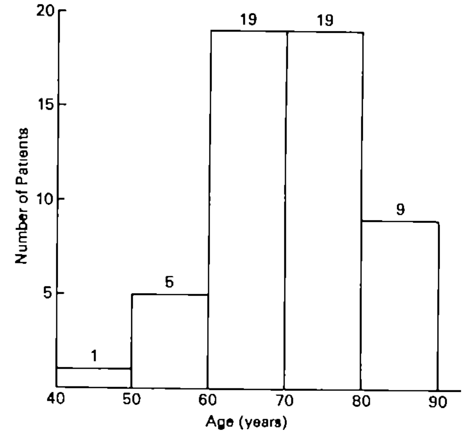

Fig. 1 Age distribution of 53 patients with invasive bladder cancer

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

in all cases, with 58% of patients having poorly differentiated tumours. For staging purposes a chest radiograph and lymphangiogram study were performed, with computed tomography replacing lymphangiography in the later patients.

After diagnosis and staging, all patients were treated by external irradiation using an 8 MV linear accelerator. The initial treatment consisted of 3840 cGy given in 16 fractions over 4 weeks to the whole pelvis using a 3-field plan with one anterior and two posterolateral fields. The patients were then rested for 1 month, following which a review endoscopic assessment was performed. Cystectomy was performed at this stage only if there was serious worsening of disease or intolerable symptoms due to radiation cystitis.

In the remaining patients where there was a good response to radiotherapy or stable disease, a further 2460 cGy in 10 fractions over 2½ weeks was given to a reduced volume including the whole bladder and original tumour field.

After a further rest period of 1 month these patients were again cystoscoped, with the option of cystectomy for those patients with persistent invasive tumour or severe radiation cystitis.

Results

Three patients died shortly after commencing treatment. The cause of death was not related to the bladder tumour in two patients, while the third patient died in renal failure due to tumour obstruction of a solitary kidney.

After treatment with 3840 cGy in 50 patients, 41 (77%) showed a favourable tumour response or no significant worsening of disease. In 7 (13%) of these patients, however, severe "small bladder" symptoms had developed due to radiation cystitis (mean bladder capacity 118 ml), and cystectomy was performed at this stage. Histological examination of the bladder specimens showed severe irradiation changes in all bladders, with persistent invasive tumour, without evidence of nodal involvement in four specimens. Of the remaining 9 patients at this stage, 6 (11%) showed significant worsening of disease but were considered unfit or unsuitable for surgery, while the remaining 3 patients with persistent disease declined any further treatment.

The planned course of radiotherapy was completed in 34 patients (64%). On cystoscopic examination no evidence of residual tumour was found in 20 of these (58.8%), although after a follow-up period ranging from 1 to 7 years (mean 3 years) 6 of these patients have presented with local recurrence or distant metastases.

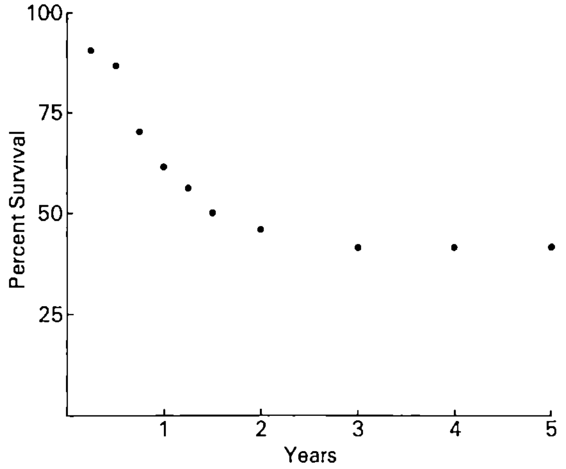

Fig. 2 Five-year survival for invasive bladder cancer treated by radical radiotherapy, with cystectomy for residual or recurrent disease, or complications of treatment

Cystectomy was performed on a further 5 patients on completion of radiotherapy. The indication for cystectomy was again "small bladder" symptoms (mean bladder capacity 95 ml), and histological examination showed post-radiation changes in all specimens, with residual tumour in only one.

The remaining 9 patients all had residual tumour and while 2 of these declined the offer of surgery, palliation only was considered for the remaining 7.

The overall 5-year survival rate (42%) has been calculated using the methods of Peto *et al.* (1976) (Fig. 2).

The operative mortality rate was 8.3%. This patient died from overwhelming sepsis 18 days following cystectomy after 3840 cGy. In addition, two patients developed a fistula after operation and required further surgery.

Discussion

The optimum treatment of locally advanced bladder cancer remains unclear. Those who favour radical surgery following limited radiotherapy point to the incidence of local recurrence that can be expected following treatment by radiotherapy alone (Hall and Heath, 1981). Moreover, it has been shown that understaging of disease may occur in up to 36% of patients with locally invasive cancer (Smith *et al.*, 1982). Equally it is suggested that cystectomy following radical radiotherapy is technically a difficult procedure with a significant degree of morbidity and mortality after operation (Whitmore, 1980). Alternatively, it can be argued that radical radiotherapy avoids the risks and trauma associated with a major operation, and the need for permanent urinary diversion in a significant number of patients with invasive bladder cancer.

It has previously been shown that survival patterns following radical radiotherapy do not differ significantly from published results using other treatment options (Wallace and Bloom, 1976; Blandy *et al.*, 1980). Our findings in this series of unselected patients support this view.

The use of computed tomography in planning the irradiation fields, and the irradiation of the whole rather than the true pelvis, help to minimise the risk of under-treatment due to staging error and additionally reduce the margin of normal tissue irradiated during the second reduced volume treatment (Adam *et al.*, 1984).

The incidence of cystectomy in this series was 22.5% with an operative mortality rate of 8.3%. None of the five patients who underwent cystectomy following radical radiotherapy died, but the post-operative morbidity in this group was significant, with two patients developing complicated fistulae.

As in previous reports, 30% of our patients showed little response to radiotherapy, and in 60% of these patients this was apparent after 3840 cGy. The poor prognosis of these patients, whatever modality of treatment is used, highlights the need to find accurate predictors of bladder tumour behaviour at an earlier stage to identify those patients for whom more aggressive (but more toxic) combined modality management may be more appropriate.

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The Authors

M O. Corcoran, FRCSI, Registrar in Urology.
D M. Thomas, FRCS, Senior Registrar in Urology.
A Lim, FRCR, Clinical Assistant in Oncology
R. J. Berry, FRCP, FRCR, Professor of Oncology.
E. J G Milroy, FRCS, Consultant Urologist

Requests for reprints to: E. J. G. Milroy, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

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Minocycline in Chronic Abacterial Prostatitis: a Double-blind Prospective Trial

P. D. SIMMONS and R. N. THIN

St Peter's Hospitals, London

Summary—In patients with chronic abacterial prostatitis, a double-blind trial of 3 months of treatment with minocycline 100 mg twice daily compared with diazepam 5 mg twice daily was undertaken.

The percentage fall in polymorphonuclear leucocyte counts in the expressed prostatic secretions was much more marked after treatment with minocycline than with diazepam. Over a follow-up period of at least 12 months, further treatment was necessary in more patients originally treated with diazepam than with minocycline.

Chronic abacterial prostatitis shows a poor response to therapy. In this condition, symptoms suggesting chronic bacterial prostatitis (including perineal, rectal or meatal pain and urinary disturbance) may be found in the apparent absence of bacterial pathogens. The condition may also be recognised in men with a history of recalcitrant non-specific urethritis (NSU) with or without prostatic symptoms. Clinical examination of the prostate is often unreliable but objective criteria for diagnosis allow rational assessment of the therapy.

Previous work suggested that patients with chronic abacterial prostatitis had polymorphonuclear leucocyte counts in the expressed prostatic secretions (EPS) in excess of 500 cells per mm^3 (Simmons and Thin, 1983). It was noted that 3 months' treatment with co-trimoxazole was followed by a fall in the EPS cell count but, without any comparison, the significance of this was unclear. Subsequently, retrospective analysis indicated that co-trimoxazole was less effective than trimethoprim or minocycline (Thin and Simmons, 1983). This report describes a double-blind trial of minocycline versus diazepam. Minocycline, like trimethoprim, is reported to enter the prostate (Hensle *et al.*, 1977; Meares, 1977); diazepam, as far as is known, has no effect on prostatitis but does allay the anxiety sometimes associated with the condition (Rosenbaum, 1982).

Patients and Methods

Forty-one men underwent investigations and entered the study. They had either symptoms suggesting prostatitis (including perineal, rectal or meatal pain, and urinary disturbance) or had had three or more episodes of NSU in the previous year. (Criteria for diagnosis of NSU were the presence in a Gram-stained urethral smear of 10 or more polymorphonuclear leucocytes in each of 10 microscope fields using the × 100 objective). All men underwent preliminary investigations to exclude active urethritis or genitourinary infection as described by Alani *et al.* (1977). This included an early morning smear and culture (Simmons, 1978), a mid-stream urine specimen and macroscopically clear first and second urine specimens. On prostatic examination there was no localised tenderness and no hardness of the prostate. The patients then underwent prostatic massage. An EPS cell count was performed by an independent observer using a Fuchs-Rosenthal counting chamber and semi-quantitative cultures were made according to the method of Leigh and Williams (1964) (Simmons and Thin, 1983). For entry to the study all EPS cell

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counts were 500 or more per mm^3 and culture showed no pathogens.

Three months of treatment was prescribed in double-blind randomised fashion—either minocycline 100 mg bd or diazepam 5 mg bd, using a double placebo. All patients were encouraged to empty the prostate by ejaculation approximately twice weekly, to drink 6 to 8 pints of bland fluids daily and to maintain a regular bowel action. Patients were seen at 6 weeks and again at 3 months, when tests were repeated. All patients gave informed consent and the protocol was approved by the local ethical committee.

Results

Twenty men started minocycline and 18 completed the treatment; 21 men received diazepam and completed the treatment. The two groups were similar in age range, marital status and country of birth for those entering and then completing the trial. Eight men in the minocycline treatment group and nine in the diazepam group had EPS polymorph counts below 500 cells per mm^3 at 3 months. Ten men taking minocycline and 12 taking diazepam still had EPS polymorph counts above 500/mm^3. The mean cell count in the EPS of men taking minocycline was 2286 before treatment, falling to 1481 after treatment (a fall of 35.2%); the figures in men taking diazepam were 2455 before treatment and 2258 after treatment (a fall of only 8%) (Table 1).

Twelve patients given minocycline and 11 patients given diazepam had symptoms on entry. At the completion of treatment, seven patients on minocycline and eight on diazepam had symptomatic improvement (Table 2). All patients taking diazepam and 16 taking minocycline had NSU prior to treatment.

Follow-up over a period of 12 to 52 months was undertaken either by examining the hospital notes (24 patients) or by means of a postal questionnaire (15 patients). All patients from both the minocycline and diazepam groups who completed treatment were traced (Table 3). Only six patients (two from the minocycline group and four from the diazepam group) had had further episodes of NSU treated. Fourteen patients taking diazepam had been prescribed antibiotic treatment for prostatitis (10 because of symptoms) compared with only 8 treated with minocycline (7 because of symptoms). Five patients treated with diazepam were referred for endoscopy because of persistent symptoms, raised EPS cell count and fears about underlying pathology, compared with only two in the minocycline treatment group. These investigations were subsequently shown to be normal in all cases. Of those patients rendered asymptomatic after trial treatment, four of seven from the minocycline group and all eight from the diazepam group had a recurrence of symptoms. One patient was withdrawn from the study because of side effects from minocycline (oesophagitis). Diazepam was well tolerated.

Table 1 Response to Treatment

	Minocycline	*Diazepam*
Mean EPS cell count before treatment	2286	2455
(±S.D.)	(1653)	(1871)
Mean EPS cell count after treatment	1481	2258
(±S.D.)	(1849)	(2243)
Fall in EPS cell count (% pre-treatment EPS)	35.2%	8.0%

STATISTICAL ANALYSIS

Comparison of EPS cell counts before and after treatment (Logarithmic transformation of data and paired 't' test)

Minocycline group	Diazepam group
$t=2.9684$	$t=2.0423$
$df=17$	$df=20$
$P<0.01$	$P>0.05$ (N.S.)

Table 2 Symptomatic Response to Treatment

	Minocycline	*Diazepam*
Symptoms improved	7	8
Symptoms unchanged	5	3
Originally asymptomatic	6	10
	18	21

Table 3 Long-Term Follow-Up

Patients	*Minocycline*	*Diazepam*
Followed up	18	21
Further NSU	2*	4
No further NSU	16	17
Prescribed further antibiotics	8	14
Previous symptoms	12	11
Symptomatic improvement	7	8
Recurrence of symptoms	4	8
Endoscoped	2	5

* Two patients treated with minocycline had no previous NSU.

Discussion

While it may be argued that treatment with an antimicrobial without isolating a pathogen is contraindicated, the presence of large numbers of leucocytes suggests a bacterial infection perhaps partly suppressed by previous chemotherapy or perhaps distal to blocked ducts. In the absence of established therapy it seemed worthwhile to initiate a prospective trial. Few antimicrobials enter the prostate; to do so, they must be lipid-soluble, low protein-binding and have a high pKa (Stamey, 1981). Minocycline yields concentrations in prostatic fluids similar to those in serum, unlike the older tetracyclines (Hessl and Stamey, 1971). It has also the advantage of a twice-daily dosage to aid compliance. Diazepam, as far as is known, has no effect on prostatitis but does allay anxiety (Rosenbaum, 1982).

Although asymptomatic improvement was similar in the two treatment groups, the improvement in the mean cell count after treatment compared with that before was much greater (35.2%) in minocycline-treated patients than in those treated with diazepam (8%). Furthermore, 14 (of 21 followed up) of the men treated with diazepam had further antibiotics compared with eight (of 18) in the minocycline group. This suggests that the natural history of chronic abacterial prostatitis as defined may be symptomatic improvement, but this does not imply resolution. We did not expect the symptomatic improvement with diazepam or we would have considered using inert placebo in its place. The importance of objective criteria for assessing the severity of prostatitis is highlighted by such apparent discrepancies and we have suggested previously that the figure of 500 polymorphs/mm^3 in the EPS is a good indication of the level of inflammatory response in the prostate and is reproducible (Simmons and Thin, 1983).

Minocycline appears to be a useful drug in the management of abacterial prostatitis. Diazepam has some symptomatic benefit and may be useful in patients with prostatodynia. These patients do not benefit from antimicrobials, have normal EPS measurements but complain of symptoms similar to those of patients with chronic abacterial prostatitis (Drach *et al.*, 1978).

However, an indication of the difficulty in managing chronic abacterial prostatitis is shown by 8 patients (5 in the minocycline group and 3 in the diazepam group) having the same symptoms after treatment, and 22 patients (10 treated with minocycline and 12 with diazepam) still having EPS polymorph counts over 500/mm^3 after 3 months' therapy. This, and the possibility of further patients with chronic abacterial prostatitis being diagnosed by the recent developments in transrectal ultrasonic scanning of the prostate, make it extremely important that further work is undertaken to find a more effective regimen for managing chronic abacterial prostatitis.

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The Authors

P. D. Simmons, MB, MRCP, Consultant Physician, Department of Genital Medicine, St Bartholomew's Hospital, London; Honorary Consultant, St Peter's Hospitals.

R N. Thin, MD, FRCPE, Consultant Physician, Department of Genitourinary Medicine, St Thomas' Hospital, London; Consultant Venereologist, St Peter's Hospitals.

Requests for reprints to P. D Simmons, St Paul's Hospital, 24 Endell Street, London WC2H 9AE

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Prophylactic Mezlocillin for Transurethral Prostatectomy

W. R. ALLAN and A. KUMAR

Department of Urology, Royal Infirmary, Bolton

Summary—In a randomised clinical trial of 100 consecutive patients treated by transurethral prostatectomy, half were given prophylactic intravenous mezlocillin. Blood cultures were obtained, the urine examined and the post-operative progress of each patient was carefully followed.

The results were analysed and a high incidence of bacteraemia and septicaemia was found. Single-dose prophylactic mezlocillin was highly effective in preventing this complication.

The presentation of septicaemia in mild and severe form is described and the aetiology discussed. Probable risk factors are identified and prophylactic and therapeutic measures described.

Peri-operative chemoprophylaxis for selected surgical procedures is widely accepted (Genster and Madsen, 1970; Kaiser *et al.*, 1978; Strachin, 1982) but discussion continues on the choice of drug or drug combination and the regime to follow (Korbel and Maher, 1976; Morris *et al.*, 1976; Shah *et al.*, 1981). Emphasis is now placed on short courses with high antibiotic concentrations (Higgins *et al.*, 1980) rather than the longer courses previously thought necessary to avoid the emergence of resistant strains.

When the sensitivity of the infecting organism is not known, as is the case in prophylaxis, the choice of antibiotic requires a spectrum as broad as is necessary but as narrow as possible. The frequency of infections with the various causative organisms in operations at particular anatomical sites gives the spectrum required and in prostatic surgery mezlocillin has been found to cover the appropriate field, including effectiveness against anaerobic infection (Issell *et al.*, 1978; Basker *et al.*, 1979). The aim of the present study was to test the efficiency of prophylactic mezlocillin in a prospective clinical trial.

Patients and Methods

One hundred consecutive patients about to undergo transurethral prostatectomy were studied, excluding only those with allergy to penicillin, those with known urinary tract infection and those who had received antibiotics in the week before surgery.

They were allocated into control and treatment groups by instructions contained in a coded and sealed letter from Bayer Co. which was opened by the anaesthetist when the patient came to theatre. Patients in the treatment group, which was unknown to medical or nursing staff, were then given 2 g intravenous mezlocillin by the anaesthetist about the time of induction of anaesthesia.

Immediately after the operation blood was obtained for culture and further blood culture was carried out on the first post-operative day and again when the urethral catheter was removed. Catheter specimens of urine were obtained before starting the operation, just after its completion, on the first post-operative day, and finally after removal of the catheter.

All patients had a full blood count and electrolyte profile performed before operation, on the first post-operative day and after removal of the catheter. Blood pressure, pulse and temperature were

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recorded 4-hourly in the initial stages and all complications were recorded.

If a patient had evidence of urinary tract or systemic infection where antibiotic therapy was required, the hospital pharmacy provided information on whether the patient had been given prophylactic mezlocillin, and appropriate management could then be decided.

Results

Details of patients in the treated and control groups are shown in Table 1. There was no significant difference between the two groups. Two important subgroups comprised patients catheterised before operation and those whose urine was found to be infected before operation in spite of admission to the trial with a sterile urine.

The results indicate that bacteraemia is common in transurethral surgery (Table 2). A positive blood culture was obtained in 20 of 100 patients undergoing prostatectomy. A statistically significant difference was seen between treated and control groups, the incidence of bacteraemia being 4 and 36% respectively.

Bacteraemia progressed to septicaemia in four patients in the control group but in no case where prophylactic cover was given (Table 4). Septicaemia developed in 8% of the control group and in 22% of patients with bacteraemia. It should be noted that bacteraemia occurs at once and that nearly all of those affected have a positive blood culture at the end of the operation.

Table 1 Details of Patients

	Mezlocillin Group	*Control Group*
Total no. of patients	50	50
Average age of patients	68.78 yrs	70.72 yrs
Pre-op catheter	8	15
Malignant prostate	5	10
Mean weight of prostatic tissue removed	19.5 g	21.5 g
Mean time taken in operation	35.2 min	34.7 min
Pre-op unknown bacteriuria	2 (both had pre-op catheter)	8 (4 had pre-op catheter)

(There were no significant differences between the 2 groups)

The presence of an indwelling catheter before operation is an important consideration in relation to post-operative bacteraemia. More patients in the control group were catheterised (Table 1) but the difference was not significant. One of 8 patients (12.5%) catheterised in the treated group and 5 of 15 (33%) in the control group gave a positive blood culture. One of the four septicaemic patients had a pre-operative catheter.

Entry into the trial required a sterile urine as judged by a mid-stream or catheter specimen of urine and no chemotherapy in the week preceding operation, and yet a catheter specimen of urine taken at cystoscopy immediately before the operation showed bacteriuria in 10 patients, 6 of whom had pre-operative catheterisation. Table 1 shows the incidence of infected urine before operation in the two groups. If there was a pre-operative infected urine, bacteraemia was extremely likely to follow operation and it occurred in seven of eight in the control group and one of two in those treated. It is significant that the organism cultured in the blood stream from the eight control patients was of the same type as found in the pre-operative urine in all cases. All four patients who developed septicaemia had positive urine cultures before operation.

Table 3 gives the incidence of post-operative bacteriuria. If infected urine was obtained on cystoscopy before operation, the infection was found in the early post-operative urine. Eleven patients had infected urine on the first post-operative day and this number had risen to 35 by the time all of the catheters had been removed. Of those who developed bacteraemia 94% also developed infection in the urine and the organism in the blood and urine was almost invariably of the same type. One would not expect a single prophylactic

Table 2 Incidence of Post-Operative Bacteraemia

Post-op Bacteraemia	*Mezlocillin Group*	*Control Group*	*Statistical Significance*
After completion of operation	2	16	$P<0.001$
First post-op day	0	4	None
After removal of catheter	0	1	None

Table 3 Incidence of Post-Operative Bacteriuria

Post-Op Bacteriuria	*Mezlocillin Group*	*Control Group*	*Statistical Significance*
After completion of operation	0	1	None
First post-operative day	1	9	$P<0.025$
After removal of catheter	9	22	$P<0.005$

dose of mezlocillin to control the development of urethritis or urinary infection but there was a marked difference in the urine culture results between the two groups, particularly in the early stages, and mezlocillin was remarkably effective in this respect.

Tables 4 and 5 give details of post-operative follow-up and complications. Septicaemia developed in four patients and it is therefore one of the more common major complications. With the help of blood culture it is not difficult to recognise. At its mildest there is simply a post-operative temperature. When more severe there is pyrexia and tachycardia combined with a fall in blood pressure in a warm patient who does not look particularly ill. In its most severe form it is catastrophic, with a cardiovascular collapse suggesting myocardial infarction. The onset can be abrupt, and treatment requires the most urgent supportive measures, including hydrocortisone and chemotherapy, if life is to be saved.

Table 6 lists the organisms isolated and, as stated, almost all of the patients with bacteraemia had infected urine, some pre-operatively and almost all post-operatively, and the organism in blood and urine was the same for each individual patient.

Table 4 Post-operative Assessment

Post-Operative	*Mezlocillin Group*	*Control Group*	*Significance*
Mean stay in hospital	7.2 days	8.02 days	None
Pyrexia >37.5°C	4	13	$P<0.05$
Rigor	1	7	$P<0.06$
Hypotension	6	7	None
Septicaemia	0	4	None
No. of patients with any complication	14	21	None
Death	0	1	None

N.B Some patients had more than one complication

Table 5 Other complications

Post-Operative	*Mezlocillin Group*	*Control Group*
Chest infection	1	3
Backache	1	1
Secondary haemorrhage	3	3
Clot retention	3	2
Nausea and vomiting	1	0
Water overload	1	0
Confusion	0	1
Sweating attack	1	0
Haematemesis and melaena	1	0
Recatheterisation	9	7

Table 6 Types of Organisms Isolated in Blood and Urine

Organisms	*Mezlocillin Group*		*Control Group*	
	Blood	*Urine*	*Blood*	*Urine*
E. coli	1	7	6	12
Proteus	0	2	1	2
Pseudomonas	0	0	0	2
Enterococci	0	2	2	12
Staphylococcus aureus	0	1	2	4
Staphylococcus albus	0	1	3	6
Streptococcus faecalis	0	0	2	1
Bacteroides fragilis	1	0	0	0
Others	0	1	5	6

NB Some organisms were isolated on more than one occasion in blood and urine in the same patient

Discussion

The results of this study confirm previous reports that bacteraemia is common following transurethral prostatectomy (Sullivan *et al.*, 1973; Robinson *et al.*, 1980, 1982). Most bacteraemic patients have a sterile urine at the onset of operation. At the end of operation they have a positive blood culture and in the early post-operative period the same organism is present in urine. This suggests that organisms or infection are present in the urethra at the time of operation and that manipulation at operation or the opening of capsular veins allows the spread of infection to the blood stream. Subsequent catheterisation quickly produces an overt urethritis from irritation and obstruction to urethral glands and the urine becomes infected.

In a few patients infection was present in the urine before operation and the incidence of bacteraemia was particularly high. Most of these patients, however, had required a pre-operative catheter for retention of urine and the source of infection was still the urethra, the urethritis which developed after catheterisation making bacteraemia and post-operative infection all the more likely. The same organism appearing in the blood stream at the end of operation and later in the post-operative urine suggested that the infection was endogenous, and the later introduction of infection or cross-infection in the ward was less common.

Working in the urethra, an unsterile area from which organisms spread to the blood stream with apparent ease, has implications for prophylaxis and one must consider the selection of patients for operation, urethral catheterisation, operative technique and chemotherapy. There is no doubt that prophylactic chemotherapy (in this study single-dose intravenous mezlocillin) given before operation is extremely beneficial.

Indwelling catheters contribute to the likelihood of bacteraemia by producing urethritis. The pre-operative catheter is there to drain urine and not blood clot and a narrow tube with a non-irritant surface should be used.

In selecting patients, the presence of urinary infection is usually a contra-indication to surgery and the infection must be treated before considering prostatectomy. Also suspect are patients with a history of prostatitis or urinary infection, and prophylactic chemotherapy should be given before operation. In this series the presence of pre-operative infection was unexpected, routine urine examination having been negative, and it is not always possible to predict patients at risk.

Preventing the spread of infection from the urethra into the blood stream also requires a careful operative technique and for patients in this series it was as follows: 20 ml of lubricant which did not contain an antiseptic were instilled into the urethra before resection. The Otis urethrotome was used and a resectoscope sheath chosen with care to avoid too tight a fit. Intermittent flow irrigation was used. Despite particular care to avoid urethral trauma there was an unacceptably high incidence of bacteraemia (36%) and septicaemia (8%) in the untreated patients. Prophylactic chemotherapy was extremely effective, reducing this incidence to 4 and 2% respectively. Two points of technique to note in relation to bacteraemia are that a prostatic resection exposes the capsule to possible fluid absorption and that the Otis urethrotome was used in all cases, perhaps opening a pathway for spread of infection to the circulation.

It is concluded that even with careful handling of the urethra, bacteraemia and septicaemia have an unacceptably high incidence in transurethral prostatectomy. Prophylactic chemotherapy is extremely effective in reducing this incidence.

The selection of patients for prophylaxis should include those with pre-operative catheters or a history of urinary infection. If one includes the unfit, those at risk from chest infection, valvular heart disease, diabetes, fitted prosthesis or simply age, prophylactic chemotherapy is mandatory for one-third to one-half of patients undergoing prostatectomy. The possibility of missing a urinary tract infection, however, makes it advisable to give prophylactic chemotherapy to all patients.

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The Authors

W. R. Allan, FRCSE, FRCS, Consultant Surgeon.
A. Kumar, FRCS, Surgical Registrar.

Requests for reprints to: W. R. Allan, Department of Urology, Bolton Royal Infirmary, Chorley New Road, Bolton BL1 4QS.

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Immunocytochemical Localisation of Prostate-specific Antigen: Specificity and Application to Clinical Practice

T. F. FORD, D. N. BUTCHER, J. R. W. MASTERS and M. CONSTANCE PARKINSON

St Peter's Hospitals and Institute of Urology, London

Summary—An immunocytochemical method to localise prostate-specific antigen (PSA) in paraffin sections was used to establish the prostatic origin of both primary and metastatic tumours.

The specificity of the technique was confirmed in 65 known primary (63 PSA-positive) and 17 metastatic prostatic carcinomas (16 PSA-positive). Thirteen non-prostatic primary carcinomas and a series of benign proliferative and malignant conditions which might be considered in the morphological differential diagnosis of prostatic adenocarcinoma were PSA-negative.

The technique has now been applied diagnostically to tumour tissue resected from 21 patients. These neoplasms of the base and neck of the bladder could not be categorised as prostatic or urothelial in origin by clinical and endoscopic assessment or by conventional histopathology. In 11 patients such tumours were PSA-positive, indicating a prostatic origin. In two further patients, the prostatic origin of lymph node secondaries was confirmed in the absence of a clinically apparent primary. The technique is a valuable adjunct to conventional histopathology.

Establishing a prostatic or non-prostatic origin for a primary or secondary neoplasm has important therapeutic implications. In most cases the clinical picture and the morphology of the tumour provide the answer, but instances remain where conventional assessments give an equivocal diagnosis. In 1979, Wang *et al.* reported the isolation and purification of an antigen from prostatic tissue which was both organ-specific and distinct from prostate-specific acid phosphatase, and subsequently shown to be a useful serum marker in patients with prostatic carcinoma (Kuriyama *et al.*, 1981; Takeuchi *et al.*, 1983). The immunocytochemical localisation (Nadji *et al.*, 1981) of this prostate-specific antigen might be used to determine the prostatic origin of a tumour. This report describes the incidence, specificity and relationship to tumour grade of PSA localisation. In addition, the technique was applied to tumours in which the cell of origin could not be specified on either clinical or histological grounds, a problem encountered particularly in tumours of the bladder neck and in secondaries of unknown primary origin.

Materials and Methods

Immunocytochemistry

The method was applied to tissue which had been formalin-fixed and paraffin-embedded in a manner standard to diagnostic laboratories. Sections from each block were stained with haematoxylin and eosin (H and E) and immunocytochemically for PSA, using a peroxidase anti-peroxidase method similar to that described by Sternberger *et al.* (1970). Using dewaxed sections, endogenous peroxidase was inhibited by a 10-min incubation in freshly prepared 0.5% hydrogen peroxide (BDH Chemicals, Poole) in methanol (BDH "Analar").

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After washing in water and then phosphate-buffered saline (PBS), pH 7.2, the sections were treated with 20% normal swine serum (NSS) in PBS for 10 min to reduce non-specific antibody binding. Subsequently, the sections were incubated at room temperature for 30 min in rabbit anti-human prostate-specific antigen antibody (Dakopatts, Mercia Brocades, West Byfleet), diluted 1:400 in 1% bovine serum albumin (BSA) (Ortho Diagnostics Ltd., High Wycombe) in PBS, followed by a PBS wash. The sections were then incubated for 30 min with the bridging antibody, swine anti-rabbit immunoglobulins, at a dilution of 1:100, followed by a further PBS wash. Rabbit peroxidase anti-peroxidase complex was then added for 30 min at a dilution of 1:100 in 1% BSA in PBS, followed by a PBS wash, before adding 0.5 mg/ml 3, 3'-diaminobenzidine free base (Sigma Chemicals, Poole) in PBS containing 1 μl/ml 100 volumes hydrogen peroxide (BDH) for 5 min. After washing in distilled water the sections were counterstained in Mayer's haematoxylin, dehydrated, cleared and mounted in Canada balsam (BDH). Negative controls were processed in an identical manner, but with the omission of each antibody.

All of the PSA and adjacent H and E sections were examined by one of the authors (MCP). In each case areas of carcinoma were defined on the H and E sections and the PSA stains assessed on the immunocytochemical preparation. The PSA was recorded as positive (Figs 1 and 2) only when brown or golden intracytoplasmic granules were seen.

Specificity of PSA Staining

Sixty-five primary prostatic carcinomas, defined morphologically and clinically, and 17 metastases from known prostatic primary tumours were stained immunocytochemically for PSA. A further 13 primary carcinomas from non-prostatic sites (bronchus, breast, stomach, large intestine, ovary, pancreas, kidney and testis) were also examined for the presence of PSA. Finally, the PSA status was investigated in other benign and malignant

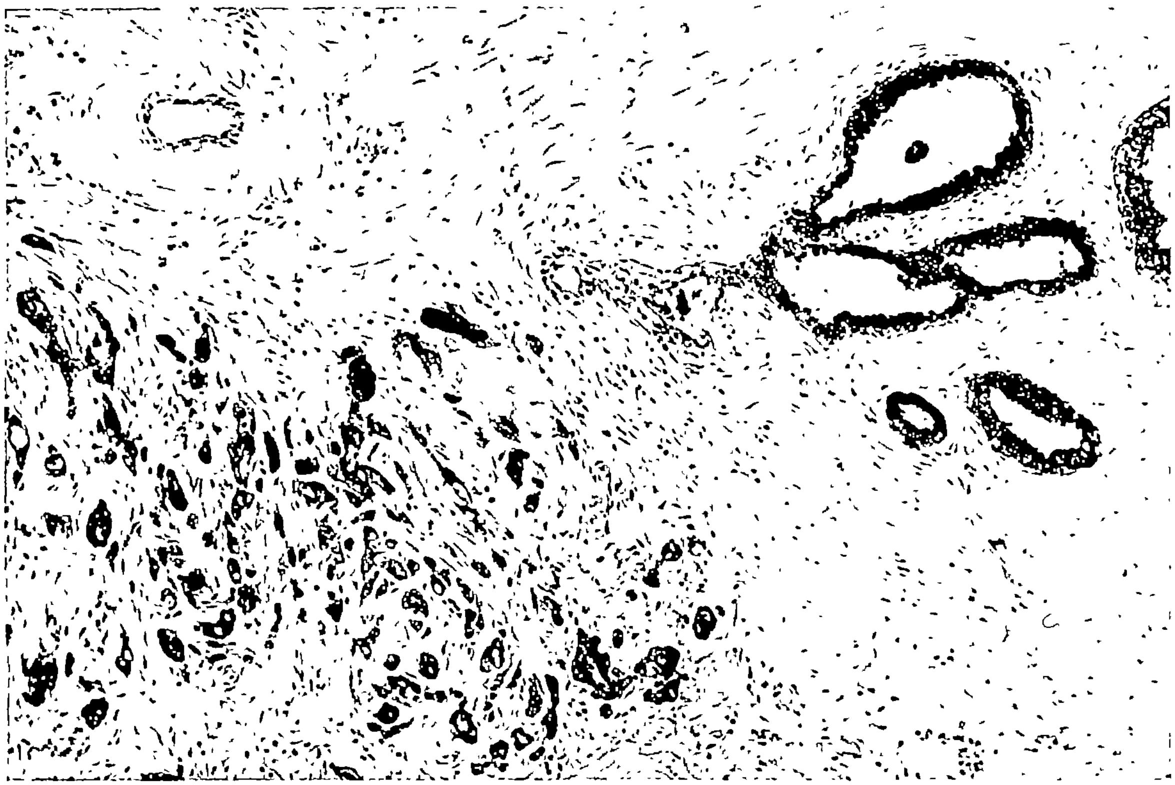

Fig. 1 PSA stain—primary prostatic carcinoma In the upper right of the figure benign acini are positive, as shown by the dark staining of the epithelial lining cells The acini are continuous with ductal epithelium which is PSA-negative The carcinoma (lower left) is PSA-positive both where cells form small glands or invade singly (Magnification ×40 Enlargement ×4.6)

conditions of bladder and prostate which might occasionally prove difficult to distinguish morphologically from primary carcinoma of the prostate.

Sensitivity: PSA Correlated with Tumour Grade

Lack of morphological differentiation frequently poses problems to the pathologist when attempting to determine the site of origin of a tumour. It was, therefore, important to correlate histological grade and PSA positivity, to see whether this marker persisted when morphology was indeterminate.

The 65 primary prostatic carcinomas were selected to represent the complete range of Gleason patterns (primary and secondary patterns 1-5) (Mellinger *et al.*, 1967). The intensity of the stain for PSA in each tumour was assessed on an arbitrary scale of 1-4 (0, +, + +, + + +), category 4 (+ + +) being equal to the intensity of staining in the adjacent benign prostatic glandular epithelium (Fig. 1). The extent of the positive stain was assessed as the approximate number of cells showing PSA positivity, again quantified on a scale of 1 (0-25%), 2 (25-50%), 3 (50-75%) and 4 (75-100%) of cells staining for PSA. Comparisons could thus be made between histological stratification and the intensity and extent of PSA positivity.

Application of PSA Staining to Clinical Practice

Twenty-one patients at endoscopy were noted to have solid, irregular tumours at the bladder neck which were palpable on bimanual examination (T2-T4). Neither the clinical findings (including intravenous urography, urine cytology and serum acid phosphatase) nor the endoscopic assessment were typical of prostatic or urothelial cancers. Histologically, such tumours proved difficult to classify because of equivocal morphology, including anaplasia or glandular metaplasia. In addition, in eight of the patients there was a past history of prostatic or urothelial neoplasia or both, thus compounding the problem.

Two further patients presented with secondary tumours (in the retroperitoneum and cervical

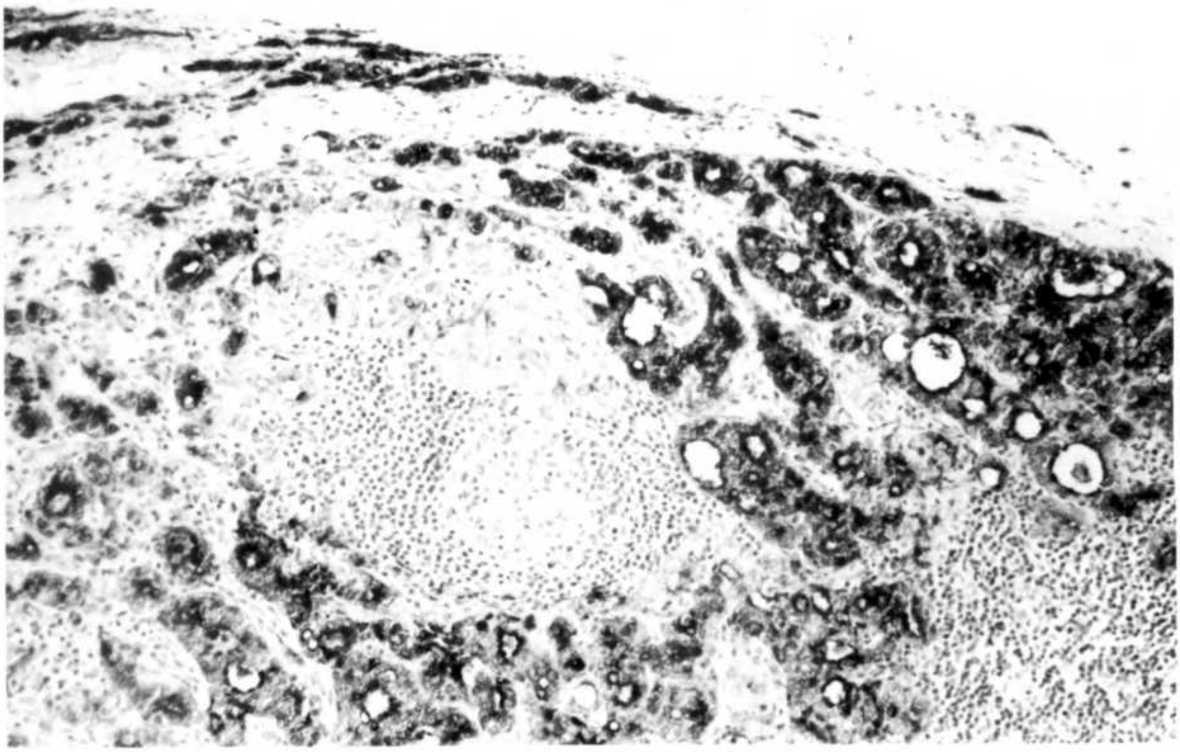

Fig. 2 PSA stain—prostatic carcinoma metastatic to lymph node. The carcinoma, invading the peripheral sinus and cortex of a lymph node, is intensely PSA-positive. (Magnification ×40. Enlargement ×4.6).

nodes) in the absence of a clinically apparent primary. Such tumours were carcinomas whose morphology did not allow the tissue of origin to be identified with certainty.

Results

Specificity

Sixty-three of 65 known prostatic primaries (97%) showed PSA-positive staining (Fig. 1), as did 16 of 17 (94%) known secondaries (Fig. 2). Non-prostatic extravesical carcinomas (bronchus, breast, stomach, large intestine, ovary, pancreas, kidney and testis), carcinomas (colon and pancreas) metastatic to bladder, urachal tumours and transitional cell carcinomas with glandular metaplasia were all uniformly negative (Table 1). Staining was not seen in the negative controls.

Sensitivity

Of the 65 primary prostatic neoplasms examined, 44 had a single pattern on Gleason grading and 21 had a double pattern, giving a total of 86 Gleason grades in 65 tumours. The relationship between Gleason grading and the extent and intensity of PSA staining are shown in Table 2. In general terms, the better differentiated the tumour, the greater was the extent and intensity of staining and vice versa.

Table 1 Specificity of PSA Staining

Prostatic Carcinomas	*PSA Positivity*
Primary	63/65 (97%)
Secondary (lymph node 12, testis 5)	16/17 (94%)
Non-Prostatic Primary Adenocarcinomas	0/13
Differential Diagnostic Problems	
Glandular and adenomatous metaplasia	0/5
TCC with glandular metaplasia	0/6
TCC invading prostatic ducts	0/2
Carcinoma metastatic to urinary tract	0/2
Urachal tumours	0/2

PSA Staining in Clinical Practice

In 8 of the 21 patients with lesions of the bladder neck, there was a past history of prostatic (4) or urothelial tumours (2) or both (2). Three of the four tumours in patients with a previous prostatic neoplasm, and neither of the two with a previous history of transitional cell carcinomas, were PSA-positive, indicating a recrudescence of their past disease. In the two patients who had both transitional cell and prostatic carcinomas in the past, the bladder neck lesion proved to be PSA-positive in one and negative in the other. All PSA-positive lesions were treated as prostatic carcinomas and all negative ones as transitional cell tumours.

In the remaining 13 patients, the tumours of the bladder neck occurred *de novo*, the patients having presented with outflow obstructive symptoms (7), obstructive uropathies (3) and painless haematuria (3) In eight patients the tumours were PSA-positive, indicating a prostatic origin, and seven were treated in a manner appropriate for a prostatic neoplasm (orchiectomy, radiotherapy, oestrogens alone or in combination). In the remaining patient, PSA staining was focal and only very weakly positive. He underwent radiotherapy and radical cystoprostatectomy since the endoscopic appearances and histology, showing an anaplastic carcinoma, were considered more in keeping with a urothelial than a prostatic neoplasm. Subsequent examination of the surgical specimen confirmed this to be a prostatic tumour.

In five patients the bladder neck tumour was PSA-negative. Four were treated appropriately for an advanced urothelial tumour (chemotherapy and radiotherapy). The remaining patient had presented with acute retention, having undergone an abdominoperineal excision of a rectal cancer a year

Table 2 Relationship between Gleason Grading of Primary Prostatic Tumours and the Intensity and Extent of PSA-positive Staining

Gleason Grade	*Number of Patterns*	*Intensity*				*Extent* (%)			
		0	+	++	+++	0-25	25-50	50-75	75-100
1	12	0	0	2	10	0	0	0	12
2	19	0	0	7	12	0	0	2	17
3	21	0	1	9	11	1	3	7	10
4	20	2	2	10	6	9	3	4	4
5	14	3	4	1	6	8	1	2	3

previously. The resected prostate (no untoward features were noted during the resection) showed benign hyperplasia and infiltration with an adenocarcinoma. Atypical morphological appearances prompted us to use the PSA staining technique which was negative. He was treated for his recurrent rectal carcinoma.

Finally, two patients presented with lymph node metastases (in the absence of a clinically overt primary tumour) in cervical nodes in one, and retroperitoneal nodes causing ureteric obstruction in the other. PSA staining was again performed because of atypical tumour morphology and both were positive. The primary carcinomas were later identified on prostatic biopsies.

Discussion

Histological diagnosis of bladder neck lesions is difficult in the presence of anaplastic tumour, glandular metaplasia in a transitional cell carcinoma, invasion of the prostate by urothelial neoplasia or metastatic carcinoma. Conventional histopathological techniques supplemented by additional information from urine cytology and serum acid phosphatase will often provide an answer. Indeed, to put the problem in perspective, approximately 1200 malignant tumours of bladder and prostate have been examined since PSA became available as a diagnostic test in the Department of Pathology and yet it has been necessary to employ it on only 21 patients.

Including the present study, 271/275 primary and 74/75 secondary prostatic neoplasms in reported series were PSA-positive and all of 222 non-prostatic lesions, of which the majority were tumours, were negative (Nadji *et al.*, 1981; Stein *et al.*, 1982; Allhoff *et al.*, 1983; Vernon and Williams, 1983; Ghazizadeh *et al.*, 1984; Purnell *et al.*, 1984). Therefore, it would appear that in 99% of tumours of prostatic origin PSA can be demonstrated and that this antigen is not found in other tissues. The five PSA-negative prostatic tumours, including three in the present series and two reported by Stein *et al.* (1982), were all associated with anaplasia.

Most workers have reported considerable variation in the number of cells which are PSA-positive (Nadji *et al.*, 1981; Allhoff *et al.*, 1983; Vernon and Williams, 1983) and in intensity of staining both between individual cells and from area to area within the same tumour. Presumably this is a result of the variable expression of antigens by tumour cells. We have attempted to express these on a semi-quantitative basis in relation to the degree of differentiation of primary. prostatic cancers. The associations were clear but some of the inconsistencies noted by other workers were seen (Vernon and Williams, 1983). As the extent of PSA staining correlates with grade, comprehensive tissue sampling may reduce the incidence of PSA-negative high grade prostate carcinomas. However, in practice the absence of PSA on a needle biopsy of high grade tumour may not be as significant as the same result on a surgically resected specimen.

The immunocytochemical detection of prostate-specific acid phosphatase (PSAP) in determining the prostatic origin of tumours is well established (Jobsis *et al.*, 1978; Nadji *et al.*, 1980). The diagnostic value of the method is limited by positive reactions in 2% of certain non-prostatic tumours and in leucocytes (Jobsis *et al.*, 1981). Comparative studies of PSA and PSAP-staining revealed conflicting results. Two studies have shown complete correlation in 30 and 37 tumours respectively (Vernon and Williams, 1983; Nadji *et al.*, 1981). Allhoff *et al.* (1983), on the other hand, found that of 19 PSA-positive prostatic tumours, only 14 were positive for PSAP. We have noted a similar inconsistency (unpublished observations). There is, of course, no reason *a priori* to expect an association and these results presumably again reflect differing specificities.

In conclusion, the immunocytochemical identification of PSA, as performed in a diagnostic laboratory on tissue processed in a routine manner, is highly specific, sensitive and associated with tumour grade. A positive PSA stain indicates that the neoplasm is of prostatic origin. When PSA cannot be demonstrated in a well differentiated carcinoma the possibility that this has a prostatic origin is remote. The failure to demonstrate PSA in an undifferentiated carcinoma makes a prostatic derivation unlikely but does not completely eliminate it. In diagnostic practice it has proved a useful technique.

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The Authors

T F Ford, FRCS, Senior Urological Registrar, St Peter's Hospitals

D N. Butcher, AIMLS, Medical Laboratory Scientific Officer, Institute of Urology.

J R W. Masters, PhD, Senior Lecturer in Pathology, Institute of Urology.

M Constance Parkinson, BSc. MD, MRCPath, Consultant Histopathologist, St Peter's Hospitals and Institute of Urology

Requests for reprints to· T. F. Ford, St Paul's Hospital, 24 Endell Street, London WC2H 9AE

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Prostatic Biopsy with the 21 Gauge Surecut® Needle. A Preliminary Report of a New Technique

S. TORP-PEDERSEN, N. JUUL, F. RASMUSSEN and M. SEHESTED

Departments of Urology and Pathology, Herlev Hospital, Herlev, Denmark

Summary—The 21 gauge Surecut® needle is a fine needle system providing regular tissue cores for histological evaluation. Using the Franzén needle sheath, transrectal biopsies were performed on 13 patients and a tissue core obtained in 12 cases.

Ultrasonically guided transperineal biopsies were performed on 14 patients and a tissue core was obtained in 13 cases. It is concluded that the 21 gauge Surecut® needle is able to yield histological material for prostatic diagnosis.

Prostatic biopsies are carried out diagnostically and as a follow-up procedure during medical or radiation therapy for prostatic cancer. Biopsies are usually taken transperineally or transrectally, guided by a finger in the rectum and by the use of large bore cutting needles under local or general anaesthesia (O'Donoghue, 1980). When transrectal ultrasound is available, very precise needle placement is possible and ultrasonically abnormal regions can be reached by the needle (Holm and Gammelgaard, 1981).

The drawback of these histological biopsies is the discomfort to the patient. General anaesthesia is often required and the method is unsuitable for repeated follow-up examinations.

In 1960 Franzén *et al.* described transrectal fine needle aspiration biopsies using a specially designed needle sheath. Patients find the method acceptable, anaesthesia is not required and biopsies can therefore be done on an out-patient basis. Evaluation of the specimens requires a skilled cytologist with a special interest in prostatic diseases and presumably because of this, the technique has not gained wide acceptance.

The Surecut® needle is a modified Menghini biopsy instrument uniting needle, stylet and syringe, and combines the advantages of fine needle biopsy, *i.e.* performance on out-patients with minimal discomfort, with those of large bore biopsies, *i.e.* regular tissue cores for histological evaluation.

Using the 23 gauge Surecut® needle we have performed fine needle histological biopsies from abdominal organs with very promising results (Torp-Pedersen *et al.*, 1984), and we wished to evaluate the suitability of the instrument in prostatic diagnosis.

Material and Methods

The Surecut® needle consists of a cutting needle with a stylet mounted on a syringe. The stylet is attached to the plunger in the syringe. When the tip of the needle is just outside the biopsy region the plunger is retracted and the stylet moves with it, revealing the cutting tip of the needle. A locking device keeps the plunger retracted and thereby maintains negative pressure. The needle is advanced into the biopsy region and a small tissue core is pulled into the needle. The needle is rotated to dislodge the tissue core and then withdrawn. The locking device is deactivated and the tissue is expelled on to sterile paper. The procedure is repeated 2 or 3 times until sufficient material has been obtained. The tissue cores are fixed in formalin and subjected to routine histological processing (Figs 1 and 2).

Using the 21 gauge Surecut® needle, which fits exactly into the Franzén needle sheath, we have performed 13 transrectal biopsies of the prostate.

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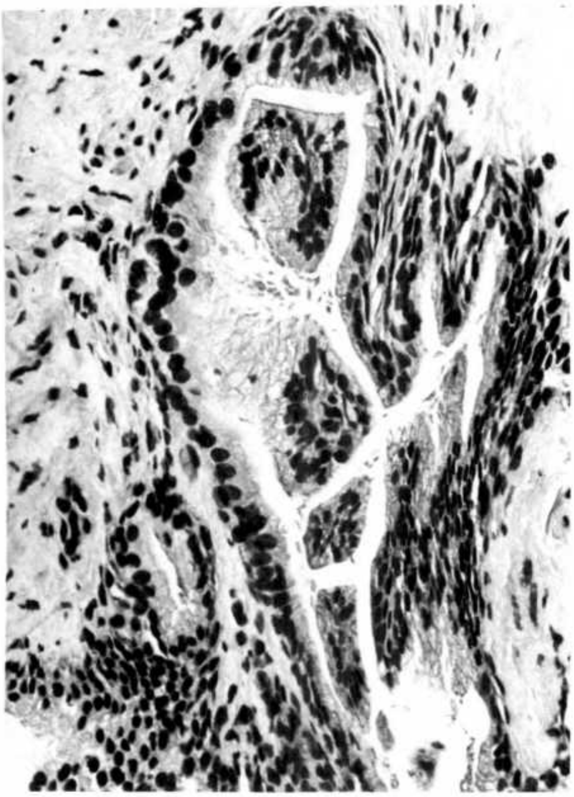

Fig. 1 Normal prostatic gland columnar epithelium (H and E × 356).

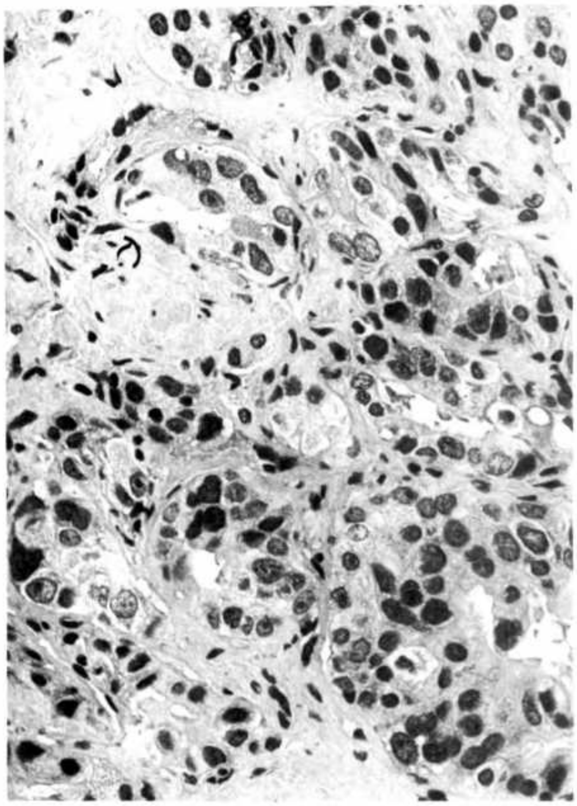

Fig. 2 Moderately dedifferentiated adenomatous epithelial cells with large irregular nuclei and distinct nucleoli (H and E × 356).

Table 1 Results of Transrectal Surecut® Biopsies

Patient Nos.	*Palpation*	*Surecut® biopsy*	*Verification*
1	Benign hypertrophy	No malignancy	TURP: no malignancy
2	Benign hypertrophy	Insufficient material	TURP: no malignancy
3	Benign hypertrophy	No malignancy	TURP: carcinoma moderately differentiated T2
4	Benign hypertrophy	No malignancy	TURP: no malignancy
5	Benign hypertrophy	No malignancy	TURP: no malignancy
6	Benign hypertrophy	No malignancy	TURP: no malignancy
7	Benign hypertrophy	No malignancy	TURP: no malignancy
8	Prostatic cancer	No malignancy	TURP: carcinoma moderately differentiated T4
9	Prostatic cancer	No malignancy	TURP: no malignancy
10	Prostatic cancer	Carcinoma moderately differentiated	Tru-Cut®: carcinoma moderately differentiated T2
11	Prostatic cancer	Carcinoma moderately differentiated	TURP: carcinoma moderately and poorly differentiated T2
12	Prostatic cancer	Carcinoma poorly differentiated	TURP: carcinoma moderately and poorly differentiated T2
13	Prostatic cancer	No malignancy	TURP: no malignancy

To obtain histological verification we selected patients about to undergo transurethral resection of the prostate. On palpation 7 patients were believed to have benign hypertrophy and 6 prostatic cancer.

We have also performed ultrasonically guided transperineal biopsies of the prostate in 14 cases using the 21 gauge Surecut® needle (Fig. 3). On palpation three patients were believed to have benign hypertrophy and nine prostatic cancer. Two patients had follow-up biopsies after implantation of radioactive seeds.

Results

Twenty-seven biopsies were performed and in 25 cases a tissue core was obtained. The results of the 13 transrectal biopsies are shown in Table 1 and the results of the transperineal biopsies in Table 2. There were no complications. Biopsy material was insufficient in one patient with benign hypertrophy and one with prostatic cancer.

Discussion

In this small series there were two cases of insufficient material. It is possible that the biopsied areas were very soft or semi-fluid, and our experience from abdominal biopsies is that such areas are very difficult to biopsy.

There were two false negative biopsies, both transrectal. One (patient 3, Table 1) was from an apparently benign gland and it is not surprising that the biopsy showed benign tissue as it was guided by palpation. The material from TURP was 75% tumour and 25% adenoma.

The other (patient 8, Table 1) was from an apparently malignant gland and the negative result

Table 2 Results of Ultrasonically Guided Transperineal Surecut® Biopsies

Patient Nos	*Palpation*	*Ultrasound*	*Surecut®*	*Verification—T stage*
1	Benign hypertrophy	Adenoma with echo-poor regions Biopsy from echo-poor regions	No malignancy	No verification
2	Benign hypertrophy	Adenoma with echo-poor regions. Biopsy from echo-poor regions	No malignancy	No verification
3	Benign hypertrophy	2 adenomas Biopsy from smallest adenoma asymmetrically located	No malignancy	TURP: no malignancy
4	Benign hypertrophy and thickening on left side	Benign hypertrophy Biopsy from left side of posterior gland	No malignancy	TURP: no malignancy
5	Prostatic cancer	Thickened posterior gland	Prostatitis	No verification
6	Prostatic cancer	Normal ultrasound. Biopsy from posterior gland	No malignancy	Tru-Cut® biopsy no malignancy
7	Prostatic cancer	Left lobe—good echo	Carcinoma moderately differentiated	Bony metastases—no TURP T2
8	Prostatic cancer	Asymmetrical gland with thickening on left side	Insufficient material	TURP: carcinoma moderately differentiated. Bony metastases T2
9	Prostatic cancer	Posterior gland slightly thickened on left	Carcinoma poorly differentiated	TURP carcinoma moderately and poorly differentiated Bony metastases T2
10	Prostatic cancer	Adenoma asymmetrically located Biopsy from thickened posterior gland	Carcinoma highly differentiated	TURP: carcinoma highly differentiated. Bony metastases T2
11	Prostatic cancer	Thickening of posterior gland on left	Carcinoma moderately differentiated	No TURP. Bony metastases T2
12	Prostatic cancer	Irregular gland with capsular defect	Carcinoma poorly differentiated	No verification T3
13	Hard prostate. Control after implantation of radioactive seeds	Small prostate with seeds	Fibrosis	No verification
14	Hard prostate. Control after implantation of radioactive seeds	Small prostate with seeds	Fibrosis	No verification

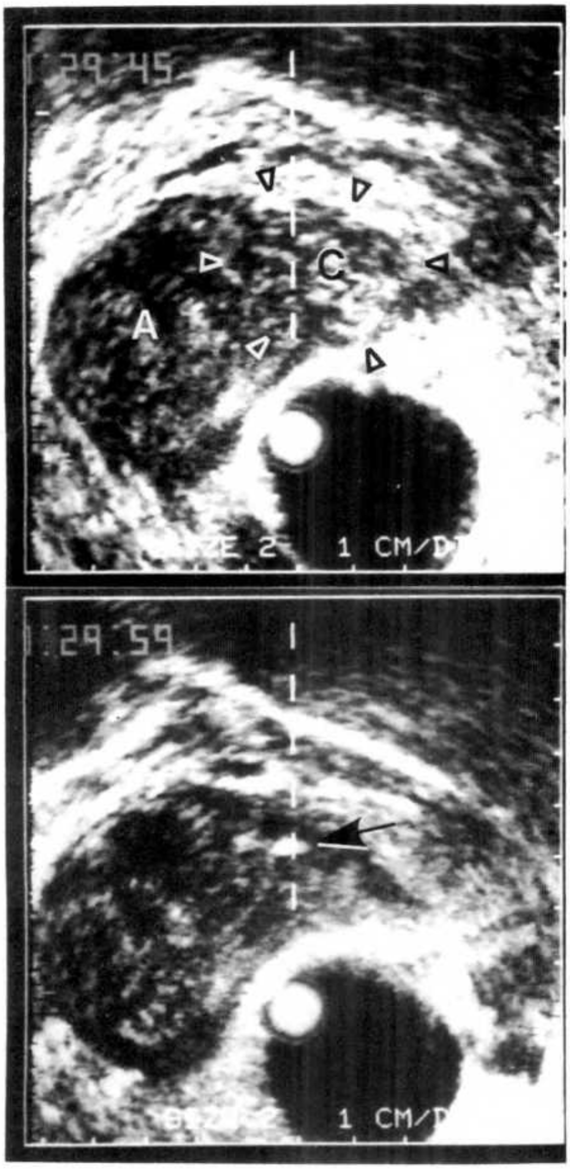

Fig. 3 (Top) Prostate with rounded adenoma (A) and thickening of the posterior gland on the left side (C). The scanner is tilted so that the puncture line transects the biopsy area. (Bottom) The needle has been inserted and as it transects the image plane a needle echo is clearly seen (arrow).

demonstrates that a needle biopsy always carries the risk of being falsely negative because only a very small fraction of the organ is removed. The material from TURP showed cancer in all specimens. It was not a complete resection and benign tissue may have been present in the posterior part of the gland which was biopsied.

In the cases of prostatic cancer where both the Surecut® and TURP/Tru-cut® had shown cancer, the degree of differentiation was similar (Tables 1 and 2). There will, however, always be greater certainty when a TURP is performed because tumours of mixed differentiation may be present.

The results of this preliminary study show that biopsy of the prostate can be performed accurately with the 21 gauge Surecut® needle. A prospective study is now being carried out to investigate the exact degree of accuracy of the method in diagnosing prostatic diseases.

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The Authors

S. Torp-Pedersen, MD, Research Fellow, Surgical Department H.

N. Juul, MD, Senior Registrar, Surgical Department H.

F. Rasmussen, MD, PhD, Chief Urologist, Surgical Department H.

M. Sehested, MD, Senior Registrar, Department of Pathology.

Requests for reprints to: S. Torp-Pedersen, Ultrasound Laboratory, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.

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Functional Bladder Neck Obstruction. Results of Endoscopic Bladder Neck Incision in 131 Consecutive Patients

M. G. CHRISTENSEN, J. NORDLING, J. T. ANDERSEN and T. HALD

Department of Urology, Herlev Hospital, University of Copenhagen, Herlev, Denmark

Summary—Endoscopic diathermy incision of the bladder neck was carried out as a routine procedure in 131 consecutive male patients with an established diagnosis of functional bladder neck obstruction. Follow-up after 3 months revealed excellent symptomatic and urodynamic results. Morbidity was low and the post-operative stay in hospital short (median 2 days). Patients must be informed of the risk of retrograde ejaculation associated with the procedure and objective evidence of the diagnosis is essential.

Functional outlet obstruction at the bladder neck level has received increasing attention during the last 20 years. In 1973, Turner-Warwick *et al.* reported the first results of endoscopic diathermy incision of the bladder neck for this condition. The prevalence of functional bladder neck obstruction (bladder neck dyssynergia) has been found to be 5% among patients referred consecutively to hospital with prostatism (Andersen *et al.*, 1979). The subjective and objective results after bladder neck incision are reported as excellent and lasting (Andersen *et al.*, 1980; Moisey *et al.*, 1982; Delaere *et al.*, 1983). However, these studies were made on a relatively small number of patients. The present study describes the morbidity and the subjective and urodynamic findings after endoscopic bladder neck incision in a large series of patients treated since the procedure was adopted as a routine in our department.

Patients and Methods

The study was retrospective and was carried out on 131 male patients treated with endoscopic bladder neck incision. The patients fulfilled the following criteria for the diagnosis of functional bladder neck obstruction. Their median age was 53 years (range 28-74). Patients with neurological disorders were excluded from the study and none had insulin-dependent diabetes mellitus.

The presenting urological symptoms are outlined in Table 1. All patients had one, and most had two or more of the symptoms listed, the combination of weak stream and frequency being the most common.

The diagnosis was based on urodynamic documentation of infravesical obstruction by uroflowmetry (n = 126; 5 had total urinary retention). The uroflowmetric result was defined as equivocal where the maximum flow rate exceeded 10 ml/s. With equivocal uroflowmetry pressure-flow studies were performed.

Table 1 Pre- and Post-operative Symptoms in 131 Patients with Functional Bladder Neck Obstruction Treated with Bladder Neck Incision

	Pre-operative (*n* = *131*)	*Post-operative* (*n* = *128*)**
Weak stream	104 (79%)	8 (6%)
Frequency	99 (76%)	21 (16%)
Nocturia	81 (62%)	11 (9%)
Recurrent infections	46* (35%)	0

* Twelve had recurrent epididymitis.
** Three were lost to follow-up.

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The pressure-flow studies on 61 patients with equivocal uroflowmetry showed uniform elevation of both the opening pressure and the maximum intravesical pressure. These pressure values were defined according to the recommendations of the International Continence Society (Bates *et al.*, 1977).

Voiding cystourethrography with serial single exposures in the straight lateral projection was also performed on 81 patients (Jacobsen and Andersen, 1982a).

The purpose of the radiographic studies was to localise the site of the infravesical obstruction to the bladder neck (Jacobsen and Andersen, 1982b). Cystourethroscopy was undertaken in all patients in order to exclude organic infravesical obstruction, *i.e.* prostatic hypertrophy, urethral stricture or fibrous bladder neck contracture. Incision of the bladder neck was carried out bilaterally at the 4 and 8 o'clock position through a resectoscope F24 or 27 using a pointed diathermy electrode. Either spinal or epidural anaesthesia was used. The incision extended from the trigone to the verumontanum, through the bladder neck and the prostatic tissue to the adventitial tissue. An indwelling catheter was left in place for 8 to 48 h.

Two patients underwent open cystolithotomy and seven had transurethral cystolithotripsy simultaneously with the bladder neck incision.

Patients were seen in the out-patient clinic 3 weeks and 3 months post-operatively, when investigations included urine culture, uroflowmetry and assessment of voiding symptoms.

Results

There was no mortality and post-operative morbidity was extremely low. Only one patient needed blood transfusion and eventually a re-operation for haemostasis. Sepsis was not encountered. Urine cultures at catheter removal showed significant bacteriuria ($>100{,}000$ colony forming units per ml) in 12 patients who subsequently received antibiotics. These 12 patients had had sterile urine pre-operatively.

The post-operative hospital stay was short (median 2 days, 95% percentile = 1-6 days).

A significant improvement in all voiding symptoms was found 3 months post-operatively (Tables 1 and 2) and 90% of patients were either subjectively cured or improved. Thirteen patients (10%) had unchanged voiding symptoms, although seven of these had an increase in maximum flow rate exceeding 15 ml/s. Only two patients had worsening symptoms. One had recurrent retention and was cured after a TURP. The other had no voiding symptoms but developed retrograde ejaculation.

Table 2 Subjective Results 3 Months after Bladder Neck Incision in 128 Patients

	No	%
Cured	96	75.0
Improved	19	14.8
Unchanged	11	8.6
Deterioration	2	1.6
Total	128	100.0

Pressure-flow measurements in the 61 patients with equivocal uroflowmetry are shown in Table 3. Only one patient with unchanged symptoms had a pre-operative intravesical pressure of 30 cm H_2O; the rest of the patients had intravesical pressures well above the normal range.

Six of 27 patients had retrograde ejaculation post-operatively. All had been informed of this risk before operation.

Uroflowmetry demonstrated a statistically significant increase in maximum flow rate from a median of 9 ml/s pre-operatively to 23 ml/s at

Table 3 Pressure Flow Measurements in 61 of 131 Consecutive Patients who had Equivocal Uroflowmetry

		Total (n=61) *median 95% percentile*	*Symptoms*		
			Unchanged (n=16) *median 95% percentile*	*Deterioration* *1*	*2*
Opening pressure	cm H_2O	100 (40-200)	115 (60-187)	190	110
Maximum micturition pressure	cm H_2O	120 (64-240)	135 (78-197)	190	130
Intravesical contraction pressure	cm H_2O	80 (22-200)	85 (32-108)	120	130
Abdominal contraction pressure	cm H_2O	5 (0-100)	45 (7-117)	0	0

follow-up (Table 4). This increase was statistically significant both for the recorded maximum flow rates ($P < 0.01$) and also when the maximum flow rates were calculated for a standard voided volume of 250 ml according to Siroky *et al.* (1979).

Table 4 Uroflowmetry in 126 Patients Before and 3 Months After Bladder Neck Incision

		Pre-operative ($n = 126$)	*Post-operative* ($n = 123$)*
Maximum flow rate (ml/s)	median	9	23
	95% percentile	(2-26)	(5-31)
Voided volume (ml)	median	240	300
	95% percentile	(65-650)	(50-900)

* Three were lost to follow-up.

Discussion

The selection of patients with functional bladder neck obstruction requires objective demonstration of infravesical obstruction in the absence of visible urethral obstruction during endoscopy. When the diagnosis has been established, surgical treatment is simple.

The fact that the procedure involves the risk of post-operative retrograde ejaculation (Andersen *et al.*, 1979; Moisy *et al.*, 1982; Delaere *et al.*, 1983) implies that objective evidence of the diagnosis is essential. All patients should be informed of this risk, particularly in view of the fact that functional bladder neck obstruction occurs in young men.

The present study has confirmed that endoscopic diathermy incision of the bladder neck for functional bladder neck obstruction can be performed safely and successfully as a routine procedure in a large number of patients.

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The Authors

M G Christensen, MD, Registrar.
J. Nordling, MD, PhD, Senior Registrar.
J. T. Andersen, MD, PhD, Senior Registrar.
T. Hald, MD, PhD, Consultant Urologist

Requests for reprints to: M. G. Christensen, Tømmerupvej 41, 4440 Mørkøv, Denmark.

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Vesico-urethral Function in Huntington's Chorea

J. S. WHEELER, D. S. SAX, R. J. KRANE and M. B. SIROKY

Department of Urology, Boston University Medical Center, Boston, USA

Summary—Six patients with Huntington's chorea (5 females, 1 male) underwent neuro-urological evaluation because of urological complaints, usually incontinence. Four patients had detrusor hyperreflexia with a normal sphincter and two patients had a normal study, suggesting that their incontinence might be non-organic. A characteristic urodynamic pattern, not previously described, was observed, consisting of choreiform contractions of the abdominal perineal floor muscles during filling with selective suppression of choreiform contractions in the perineum during detrusor contraction.

Huntington's chorea is a degenerative disease with autosomal dominant inheritance characterised by progressive neuronal cell loss in the basal ganglia (primarily the caudate nucleus) and cerebral cortex. The typical signs of dementia and choreiform movement usually appear in adult life. Genitourinary dysfunction, especially incontinence, is not rare in Huntington's chorea, although no detailed description is available in the literature. Therefore we reviewed the neuro-urological findings in six patients with Huntington's chorea referred with urological dysfunction.

Patients and Methods

Six patients (5 females, 1 male) with Huntington's chorea and urological dysfunction were referred for neuro-urological evaluation which included testing of perineal sensation, deep tendon reflexes and extensor plantar responses of the lower extremities. The urodynamic assessment included rapid fill CO_2 cystometrography (CMG) at a rate of 120 ml/min, and concomitant perineal electromyography (EMG) using a concentric needle electrode placed in the perineal striated musculature (external anal sphincter in females, bulbocavernosus muscle in males). The electromyographic activity was noted on the oscilloscope and audiomonitor and recorded on a polygraph recorder. Assessment of voluntary sphincter control, neuropathic changes and the guarding reflex was performed (Siroky and Krane, 1982). The urodynamic data were interpreted according to previously defined criteria (Krane and Siroky, 1979).

Results

The six patients had a mean age of 52 years (range 43-67) and Huntington's disease had been present for an average period of 8 years. Thus the mean age of onset was 44 years. Urological symptoms had been present for an average duration of 1.9 years (onset 6.1 years after the onset of Huntington's chorea). The urological symptoms included frequency, urgency and nocturia in all 6 patients, associated with incontinence in 5. One patient had additional symptoms of obstruction and one patient had recurrent urinary tract infection.

Other significant neurological problems included depression in five patients and dementia in four (Table). Five patients had the characteristic prominent choreoathetoid movements while one patient had the much less common rigid form of Huntington's disease and a mild distal musculature chorea (Westphal variant). The neurological examination of the lower extremities revealed normal sensation in all patients and hyperactive deep tendon reflexes in five. No patient had Babinski's sign. All patients were receiving antidepressant or neuroleptic medication at the time they were studied (Table).

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Table Details of Patients

Sex	*Disease present (years)*	*GU symptoms present (years)*	*GU symptoms*	*Other symptoms*	*Neuro. signs*	*Medication*	*Sensation*	*Reflexes (Babinski)*	*CMG*	*EMG*	*Treatment*
F	8	6 mo.	Incontinence Irritative	Dementia Depression	Chorea	Haloperidol Imipramine	+	3+ (−)	Normal	Normal	Anticholinergic
F	2	2	UTI Irritative	Depression	Chorea	Lithium	+	3+ (−)	Normal	Normal	Anticholinergic
F	7	1	Incontinence	Depression	Chorea	Fluphenazine	+	3+ (−)	Detrusor hyperreflexia	Voluntary control	Anticholinergic
F	10	2	Incontinence Irritative	Dementia Depression	Chorea	Haloperidol Propantheline	+	3+ (−)	Detrusor hyperreflexia	Voluntary control	Anticholinergic
F	5	1	Incontinence	Dementia Depression Dysphagia	Rigidity	Amitriptyline Amantadine	+	3+ (−)	Detrusor hyperreflexia	Normal	Indwelling catheter
M	15	5	Incontinence Irritative Obstructive	Dementia	Chorea	Haloperidol	+	2+ (−)	Detrusor hyperreflexia	Voluntary control	TURP Anticholinergic

The urodynamic examination showed detrusor hyperreflexia without sphincteric dyssynergia in 4 patients and normal vesico-urethral function in 2. No cases suggestive of neuropathy were detected by EMG. All patients demonstrated preservation of the guarding reflex. However, 3 of the 4 patients with hyperreflexia had poor voluntary control as revealed by perineal EMG. Interestingly, the patient with predominance of rigidity had normal voluntary control of perineal musculature while the choreic patients had diminished voluntary control.

A representative urodynamic tracing is shown in the Figure. The effect of the choreiform movement is manifested by the seemingly random, brisk CMG spikes, representing a rapid change of intra-abdominal pressure secondary to the involuntary trunk and respiratory motion. One may also note simultaneous EMG discharge in the perineal muscles. This patient had a normal study, with normal bladder sensation, urge and contraction with appropriate sphincteric relaxation at a volume of 350 ml. It is noteworthy that the involuntary

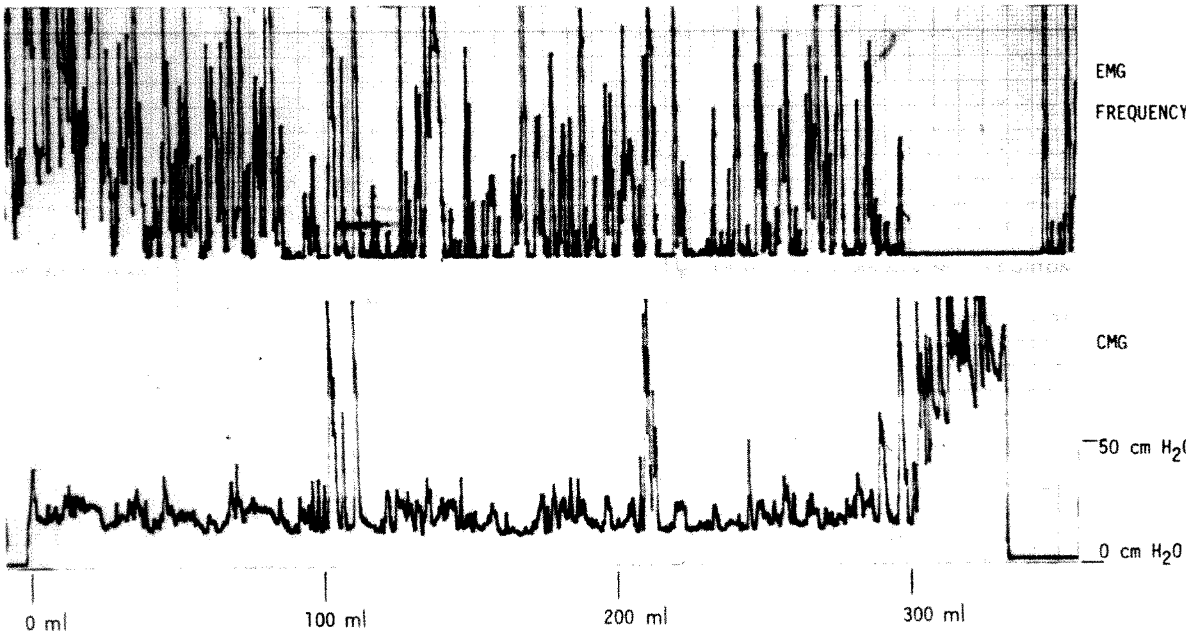

Fig. Cystometrogram—perineal electromyogram in a 46-year-old female patient with Huntington's chorea. The EMG is presented as a relative scale with full deflection representing maximum contraction.

contractions of the perineal musculature are suppressed during detrusor contraction even while the choreiform abdominal movements continue. Following release of the detrusor contraction, the perineal contractions immediately resume. The same phenomenon was observed in all five patients demonstrating chorea but not in the patient with rigidity.

Discussion

The diagnosis of Huntington's chorea is based on the triad of dementia, chorea and a positive family history (Heathfield, 1973). Early in the illness there is a prodrome of personality change, depression and sexual dysfunction (Shoulson and Chase, 1975). The dementia is progressive, often accompanied by severe depression. These mental changes can lead to neglect of hygiene and apathy toward social norms of urinary control. This type of incontinence is difficult to differentiate from that due to detrusor hyperreflexia. The choreoathetosis develops insidiously and includes facial tics, repetitive utterances, dysarthria, dysphagia, abnormal ocular motility, abnormal girdle, trunk and extremity movement, and a dance-like gait. This movement increases with voluntary action and decreases with sleep. Some patients may develop a form of rigidity similar to that of Parkinson's disease (Hayden, 1981) late in their illness, with hypokinetic rigidity and mask-like facies as seen in one of our patients.

The mean age of onset of this disorder is 38 years, with both sexes affected equally. The illness lasts an average of 16 to 20 years and the average age at death for the mid-life onset group is 55 to 60 years. Death occurs from dysphagia leading to aspiration of food, infection and/or suicide, especially in younger patients. The pathology at autopsy is neuronal cell degeneration in the neostriatum with increased numbers of astrocytes, resulting in dilatation of the ventricles and frontal lobe atrophy (Bruyn, 1968).

The mean age at onset in our series was 44 years and urinary symptoms were first noted an average of 6.1 years after onset. Since the illness has an average duration of 15 to 20 years, it would appear that urinary incontinence is a feature of the middle and late stages of the disease. Urinary dysfunction in Huntington's chorea is only rarely mentioned in the literature. For example, Bruyn (1968) states, "Many patients, at one stage or other of the disease, show urinary incontinence . . . impaired sphincter control certainly is more frequent than is generally supposed." Hayden (1981) estimated that 20% of patients with Huntington's chorea become incontinent of urine and faeces, usually later in the course of the illness.

The low incidence of voiding symptoms was also noted by Sax *et al.* (1973). This may be due to the anticholinergic effects of neuroleptic agents often used in treatment and the fact that these patients were generally younger than the present group. For example, in Sax's series of 10 patients, 6 had "hypotonic" CMGs typical of a "motor paralytic bladder", with large volumes of residual urine and few symptoms. His series included only one patient described as having a "spastic bladder". This patient was not receiving therapy at the time.

The diagnosis of Huntington's disease is made clinically. Pyramidal tract dysfunction occurs in 30% of patients and many become hyperreflexic, but only 10% demonstrate Babinski's sign (Bruyn, 1968; Hayden, 1981). Almost all patients in our series had hyperactive deep tendon reflexes but none had Babinski's sign. In addition, computerised tomography can demonstrate atrophy of the caudate nucleus and putamen (Sax *et al.*, 1983). Poor carbohydrate metabolism is also frequently found (Shoulson and Chase, 1975). Various biochemical parameters may be useful in detecting the disease in the future, especially with the elucidation of the physiology of dopamine. Drugs which increase dopamine concentration in the brain can cause choreiform activity not only in patients who are at risk by family history (Heathfield, 1973) but also in patients with Parkinson's disease who are treated with dopaminergic agents.

Our series concerned only patients with urological complaints. The irritative symptomatology and incontinence in four of our patients can probably be ascribed to detrusor hyperreflexia. Incontinence in patients with a normal CMG may be due to dementia (frontal lobe incontinence), depression and/or inability to assist themselves to the toilet.

Detrusor hyperreflexia results from interference with the normal inhibition of the pontine micturition centre by higher centres (Siroky and Krane, 1982). In Huntington's disease the function of the pontine centre is preserved, as shown by our observation that choreiform contractions in the perineum (but not in other somatic muscles) are suppressed during micturition. This is a result of the powerful and selective inhibitory effect of the pontine micturition centre on the anterior horn cells of the sacral spinal cord during detrusor contraction. A further illustration of the same phenomenon is afforded by one's almost total inability to elicit the bulbocavernosus reflex during normal micturition.

Anticholinergic agents can alleviate the urological symptoms but treatment of the underlying disorder remains difficult. Dopamine-depleting or blocking agents, such as reserpine, haloperidol or phenothiazines, are used with some success to control choreiform activity. These agents have anticholinergic side effects and may suppress the detrusor hyperreflexia as well.

In summary, Huntington's chorea is associated with detrusor hyperreflexia in some patients but symptomatic patients may have normal urodynamics. Although chorea is the hallmark of the disease, we have found that normal suppression of the perineal muscles occurs in these patients during voiding. Thus sphincteric obstruction is not a problem in Huntington's chorea.

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The Authors

J. S. Wheeler, Jr., MD, Fellow in Neuro-urology
D S Sax, MD, Professor of Neurology.
R. J Krane, MD, Professor of Urology.
M. B. Siroky, MD, Associate Professor of Urology

Requests for reprints to. M. B. Siroky, 75 E Newton Street, Boston, MA 02118, USA.

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Abnormal Electromyographic Activity (Decelerating Burst and Complex Repetitive Discharges) in the Striated Muscle of the Urethral Sphincter in 5 Women with Persisting Urinary Retention

CLARE J. FOWLER and R. S. KIRBY

Reta Lila Weston Institute of Neurological Studies, Middlesex Hospital Medical School; Department of Urology, Middlesex Hospital, London

Summary—In five women with urinary retention, recordings from the striated muscle of the urethral sphincter revealed highly abnormal electromyographic (EMG) activity. Using a concentric needle electrode, recordings revealed very striking bursts of activity, referred to here as decelerating burst (DB) and complex repetitive discharges (CRD). Such EMG activity is exceedingly unusual in skeletal striated muscle and resembles most closely the rarely encountered condition of "pseudomyotonia".

We suggest that this abnormal activity is associated with a failure of relaxation of the striated muscle of the urethral sphincter, which results in chronic retention.

Unexplained urinary retention in women is not uncommon but its cause is unknown. Among several hypotheses advanced (Blaivas and Labib, 1977), one suggestion is that there may be a failure of relaxation of the urethral striated muscle (Raz and Smith, 1976). We were therefore interested to discover an EMG abnormality which may indicate an underlying failure of relaxation of the striated urethral muscle in five women with persisting retention of urine.

Patients and Method

EMG of the striated muscle of the urethral sphincter was recorded with a concentric needle electrode introduced percutaneously (Fowler *et al.*, 1984).

Case Reports

Case 1. A. R., a 41-year-old former nurse, presented in 1983. She had a history of recurrent cystitis since the age of 10. After a hysterectomy at the age of 38 she had suffered from bouts of urinary frequency which would last for several days, followed by several days during which she would pass urine with great difficulty, "in dribbles" In the past she had been treated for agoraphobia and depression.

Neurological examination was normal. Cystoscopy revealed a large capacity but otherwise normal bladder. Urodynamic testing demonstrated a residual volume of 300 ml and a filling volume of 1300 ml. She was unable to void during the study.

She was managed over the ensuing 18 months with alternating periods of self-catheterisation and an indwelling suprapubic catheter, but on account of recurrent urinary tract infections an ileal conduit became necessary.

Sphincter EMG was recorded on four separate occasions, and on a fifth occasion when the patient was under general anaesthesia.

Case 2. J.N., a 58-year-old multiparous housewife, was referred in 1981 with infrequent, painful voiding. She had had multiple urinary tract infections since childhood. On direct questioning she admitted she had always voided infrequently, only 3 times in 24 h as a child.

At the age of 38 she had a hysterectomy and following this she found she voided only once or twice in 24 h. Investigations then showed she had a large and poorly contractile bladder.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

Neurological examination was normal. Cystoscopy revealed a large capacity, infected bladder. On urodynamic testing her bladder emptied incompletely with a micturition pressure of 40 cm of water. This pressure was poorly sustained, leaving a residual volume of 200 ml. The flow rate never exceeded 12 ml/s and the radiological appearance of the urethra was reported as being "possibly a little tight".

Since her hysterectomy she had had seven urethral dilatations, all without any lasting benefit. She managed for 2 years with intermittent self-catheterisation but suffered recurrent urinary tract infections and required long-term suprapubic catheterisation, and then more recently an ileal conduit.

Urethral sphincter EMG studies were carried out on four separate occasions.

Case 3. K.W., a 41-year-old multiparous housewife, was referred in 1979 on account of recurrent retention and urinary tract infections. She first had retention following a cystoscopy in 1973. Urodynamic studies elsewhere were reported as showing no intravesical pressure rise during filling and a voiding pressure of 50 cm of water, which was poorly sustained, with a poor flow rate and large residual volume.

On direct questioning she had been unaware of voiding difficulties but had passed urine only 2 to 3 times a day and "never went often as a child".

She was examined by a neurologist and seen by a psychiatrist, neither of whom found the cause of her voiding difficulties

In spite of several urethral dilatations she continued to complain of voiding difficulties. Self-catheterisation was followed by long-term suprapubic catheterisation. In 1981 an ileal conduit became necessary.

Urethral sphincter EMG recordings were made on four separate occasions.

Case 4. M.M., a nulliparous, 22-year-old female, presented in 1977 with dysuria and frequency. On direct questioning she said she had had recurrent episodes of dysuria and frequency with suprapubic and back pain since the age of 16. She had noticed a slow urine stream and had found double micturition was sometimes necessary. These difficulties with bladder emptying were usually worse in the morning

Repeated urodynamic investigations showed a residual volume greater than 200 ml and a flow rate that never exceeded 10 ml/s. A myelogram was performed and this was normal.

In 1977 urethral dilatation was performed twice but with no long-lasting benefit. Whilst in the ward she complained of back pain and loin pain but repeated urine cultures were sterile.

Up to the present time she has remained well, voiding by a combination of abdominal straining and intermittent self-catheterisation.

Urethral sphincter EMG was recorded on 2 separate occasions.

Case 5. C.McK., a 28-year-old nulliparous female, was admitted in February 1984 with a 2-day history of painless urinary retention. She had been unaware of any previous urinary symptoms, although on direct questioning she admitted to infrequent voiding (3 times in 24 h).

She was examined by a neurologist, who found no abnormality.

She was catheterised and found to have a residual volume of 700 ml. Although she was able to void following removal of the catheter, she returned in retention in June 1984. On this occasion removal of the catheter failed to re-establish micturition. Urethral sphincter EMG was highly abnormal.

She was treated with oral phenytoin 100 mg b.d. and an indwelling catheter was left in for 2 weeks. At the end of that time sphincter EMG recording was normal and she was able to void when the catheter was removed.

Results

Using standard neuro-electrophysiological recording equipment and a concentric needle electrode, EMG activity can be both heard and visualised. In the five patients described here, bizarre burst discharges were superimposed on the normal tonic background motor unit activity. These bursts have a characteristic sound and are very easily recognisable (Fig.).

When the discharges fired at a decelerating rate we termed the activity "decelerating bursts" (DBs); when firing at a steady rate, such discharges were referred to as "complex repetitive discharges" (CRD) (Dyro *et al.*, 1983). DBs were the most striking feature of these recordings both in terms of prevalence and auditory impact.

When the needle was in close proximity to a decelerating burst discharge generator, the activity had a characteristic, highly mechanical sound, with a decelerating quality. This sound is very much like that made by a rally motor cycle when it slows to go round a corner. When the needle was further from the sound generator the sound has been said to resemble that "of the underwater recording of a chorus of whales" (Butler 1979). CRDs recorded distantly have a "growing" quality, but otherwise have the usual characteristics of a repetitively firing polyphasic motor unit.

DBs and CRDs were recorded on every occasion in each patient (with the exception of Case 5 after treatment with phenytoin). In some cases, particularly Case 1, DBs could be heard distantly on first inserting the needle electrode, before sharp motor unit activity was recordable.

Spontaneously occurring DBs and CRDs were heard in each case, although these abnormal bursts

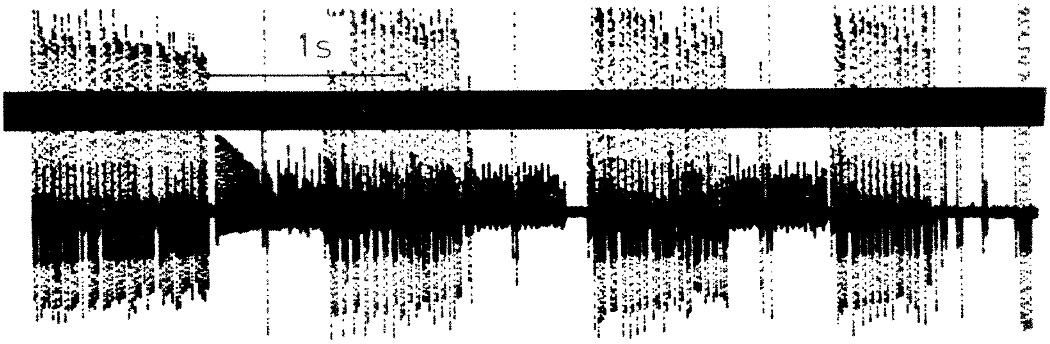

Fig. EMG recording of decelerating burst and complex repetitive discharges as they may appear on the oscilloscope screen with a slow time base.

were more profuse in some patients (Cases 1, 4 and 5) than in others. In Case 2, CRDs were a more prominent finding than DBs. At all recordings it was found that the abnormal burst activity could be accentuated by coughing, straining, leg movement or movement of the recording electrode needle.

Sphincter EMG was recorded from Case 1 when she was under general anaesthesia. Initially anaesthetised without neuromuscular blocking agents, tonic motor unit activity and some DB activity could be heard when skeletal striated muscle was electrically silent. With curarisation this activity eventually faded, but only some minutes after intubation had become necessary.

Discussion

Significance of Decelerating Burst and Complex Repetitive Discharges

The decelerating quality of this activity is highly reminiscent of the sound recorded from striated skeletal muscle in the condition known as dystrophia myotonica. However, in that condition the activity is due to the repetitive discharge of individual muscle fibres. In the cases described here, the repetitive firing is of motor units or fractions of motor units. For this reason the activity can be considered electrophysiologically most like that described by Hughes and Matthews (1969) which they termed "pseudomyotonia" but which was first described by Isaacs (1961) as a syndrome of "continuous muscle fibre activity". There is, however, such confusion surrounding the various EMG findings associated with Isaacs' syndrome or "pseudomyotonia" (Willison, 1982) that these terms have been abandoned. Instead a purely descriptive term, emphasising the striking auditory quality of the activity, has been adopted: decelerating burst discharges.

Both myotonia and pseudomyotonia are associated with a failure of relaxation of the muscle in which it is occurring.

Hypothesis

We suggest that the EMG activity described here indicates an underlying impairment of normal relaxation of the striated component of the urethral sphincter. This failure of normal relaxation leads to outflow obstruction and eventually to overdistension of the bladder, presenting in its terminal stages with the clinical picture seen in Cases 1 to 4.

Although four patients had had multiple urethral stretches in an attempt to alleviate their symptoms, the fifth had not. This makes an alternative hypothesis that the activity is simply the result of iatrogenic damage to the innervation less likely.

However, DBs and CRDs have not been found exclusively in patients with urinary retention. We have recorded profuse DBs and CRDs in two patients who were not in retention at the time of recording. One was an elderly woman with recurrent urinary tract infections. The other was a young girl presenting with severe loin pain suggestive of pyelonephritis but in whom urinary cultures were sterile. CRDs have also been reported in a paediatric population (Dyro *et al.*, 1983) in a variety of clinical conditions. The three patients in the report of pseudomyotonia by Butler (1979) were incontinent.

One possible explanation for these observations is that if retention with a large acontractile bladder is the terminal stage of this condition, other types of micturition disorder would be expected while the urodynamic changes of the final state were evolving.

Phenytoin has proved to be curative in the treatment of Isaacs' syndrome or "pseudomyotonia" in skeletal striated muscle (Isaacs and Heffron, 1974). If it is conclusively demonstrated that the EMG abnormality we have described is associated with a significant failure of relaxation of the urinary sphincter, treatment with phenytoin may prove to be effective if given early enough. The response of Patient 5 is encouraging, but a double-blind trial of phenytoin in patients with abnormal EMG activity and persisting urinary retention is required.

Detailed urethral pressure profile studies of these patients are now in progress.

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The Authors

Clare J Fowler, MSc, MRCP, Senior Registrar in Clinical Neurophysiology, Middlesex Hospital.

R S. Kirby, FRCS, Senior Registrar in Urology, Middlesex Hospital.

Requests for reprints to Clare J. Fowler, The Reta Lila Institute of Neurological Studies, Middlesex Hospital Medical School, Mortimer Street, London W1N 8AA

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Management of Congenital Posterior Urethral Valves

J. E. S. SCOTT

Department of Surgery, University Medical School, Newcastle upon Tyne

Summary—A series of 46 children treated by the author since January 1972 for congenital posterior urethral valves is presented: 22% were diagnosed at birth, 28% as neonates and 52% in the first 3 months of life.

Ninety-three per cent had unilateral or bilateral dilatation of the upper urinary tract at the time the valves were diagnosed and 72% had ureteric reflux. Unilateral reflux occurred into the left ureter twice as often as the right. Renal failure was present at the time of diagnosis in 72% of all of the children but in 83% of those aged less than 3 months.

Surface urinary diversion was used minimally during post-operative management and contributed little to the recovery of renal function. Reflux disappeared spontaneously in one-third of the refluxing ureters. Ureteric dilatation subsided spontaneously in 57% of dilated ureters. Surgery was performed mostly for reflux. Non-refluxing ureteric dilatation was made worse by surgery in a few instances and in others the dilatation improved with time rather than as a result of surgery.

Renal function returned to normal in over 60% of the children who were in renal failure at diagnosis. Measurement of glomerular filtration rate was the most accurate method of predicting recovery of renal function: a value of less than 50% of normal for age at the time of diagnosis forecast persistent chronic renal failure with all its attendant complications.

Posterior urethral obstruction caused by congenital urethral valves is a recognised entity, the diagnosis and surgical treatment of which are well defined and straightforward. It is the sequelae of the obstruction about which there is still some disagreement over management: of particular concern are ureteric reflux, ureteric dilatation and renal failure.

The purpose of this study was to describe a consecutive series of children treated for congenital posterior urethral valves since January 1972. This particular year was chosen because the documentation and biochemical investigation of the patients since that date were more comprehensive than previously. Special emphasis has been laid on the manner in which ureteric reflux and dilatation were treated and the predictive value of renal function tests in determining the eventual degree of recovery in renal function that can be anticipated.

Patients and Methods

Age at Diagnosis There were 46 children whose age at diagnosis is given in Figure 1. Nearly 22% were diagnosed at birth, 28% as neonates and 52% in the first 3 months. Amongst the older children were two 9-year-olds with a lifelong history of straining to pass urine and a poor stream which had never been recognised as abnormal by them or by their parents. One of these boys lived in a small secluded rural community and his only companion was his sister. The other boy had an unstable domestic background. Both presented with acute retention with overflow.

Presentation Symptomatology and physical signs fell into two groups, namely obstructive (straining, poor intermittent stream, dribbling, palpable bladder) and infective (septicaemic shock, poor feeding, abdominal pain, positive urine culture). Eighteen (39%) had obstructive symptoms and 26 (56.5%) infective. Two other children had neither; they were failing to thrive but had sterile urine. It is

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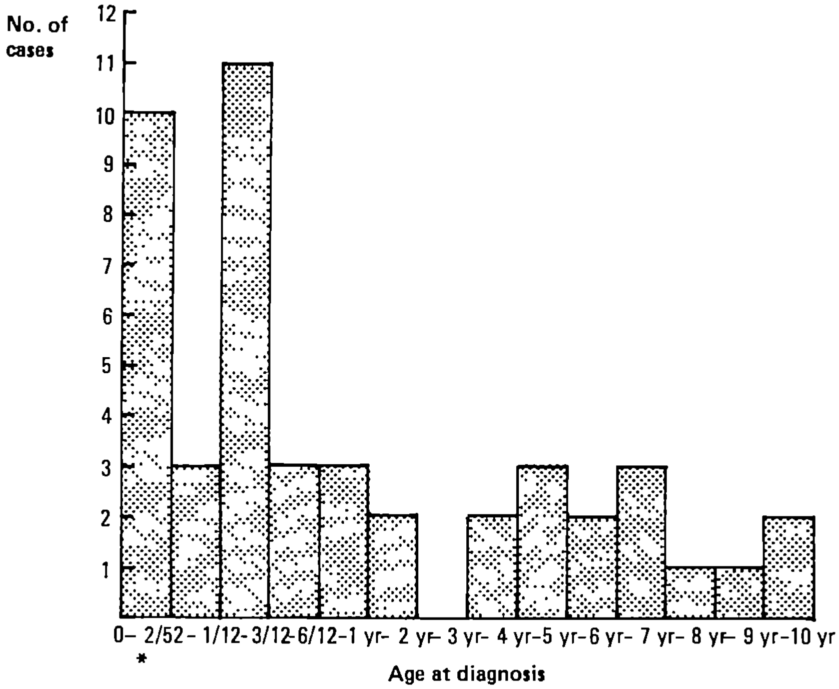

*2 diagnosed in fetal life

Fig. 1 Age at diagnosis.

noteworthy that of 13 neonates, 10 (77%) had obstructive symptoms, whereas of 33 aged more than 1 month, 25 (78%) had infective symptoms.

Results of Primary Investigation In every case the valves themselves were diagnosed by micturition cystourethrography (MCUG). The upper urinary tract was examined by intravenous urography (IVU) in 36 children and by renal ultrasound (US) in 11. Neither method was used in three cases because bilateral reflux adequately displayed the upper tract. There is little point in performing IVU on newborn infants because demonstration of the urinary tract is poor at best and when renal failure is present there is none. Renal US is the method of choice. Thirty-two children (69.5%) had bilateral upper tract dilatation and 11 (23.9%) unilateral; 1 of the latter had a solitary kidney.

Ureteric reflux was present in 48 ureters (52.7%) but in 33 children (71.7%), in whom it was bilateral in 15 (32.6%). In the children with unilateral reflux, the left side was affected twice as often as the right, a discrepancy also noted by Hoover and Duckett (1982). If, as has been suggested by Henneberry and Stephens (1980), the ureteric reflux is caused by an excessively lateral origin of the ureteric bud from the mesonephric duct during embryological development, there is no apparent reason why this should occur more commonly on the left side.

Renal Function at Time of Diagnosis This was estimated by measuring plasma urea and creatinine concentrations, plasma bicarbonate levels and glomerular filtration rate (GFR). The latter was determined from creatinine clearance values adjusted to a surface area of 1.73 m^2. GFR was also calculated from the plasma creatinine concentration and the child's length according to the formula propounded by Counahan *et al.* (1976); GFR (ml/min/1.73 m^2) = height(cm) × 38/plasma creatinine (µmol/l)-12.4. A plasma creatinine concentration of between 100 µmol/l (1.2 mg/100 ml) and 200 µmol/l (2.4 mg/100 ml) and/or a urea concentration of between 5 mmol/l (30 mg/100 ml) and 10 mmol/l (60 mg/100 ml) were taken to indicate moderate renal failure. Levels above these figures indicated severe renal failure. Plasma bicarbonate levels between 18 and 15 mmol/l (180 and 150 mg/100 ml) indicated moderate metabolic acidosis and, below these figures, severe metabolic acidosis. It was necessary to compare GFR with normal values for age (Fig. 2). At birth, GFR in a

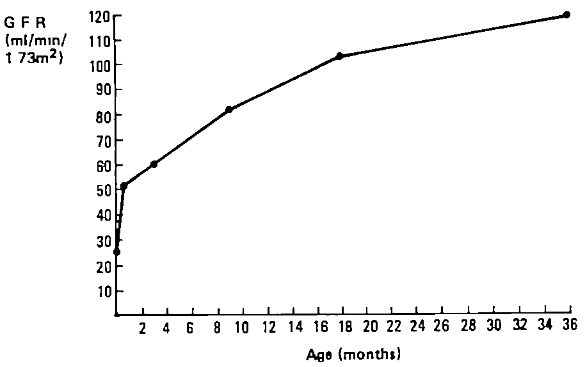

Fig. 2 GFR by age (full-term mature baby).

full-term mature baby is approximately 25 ml/min/1.73 m^2 but doubles in the first 10 to 12 days of life. Thereafter the rate gradually increases to adult values at 3 years. A rate of >50% of normal was regarded as moderate depression and <50% severe depression. Table 1 shows the biochemical findings. Thirty-three children (71.7%) had biochemical evidence of moderate or severe renal failure and of these 20 (60.6%) were diagnosed below the age of 3 months. In other words, the incidence of renal failure in children under the age of 3 months was 83%.

Table 1 Posterior Urethral Valves. Renal Function at Diagnosis

Abnormality	*HCO_3*	*Plasma urea*	*Creatinine*	*GFR*
None	27 (62.8)	17 (37)	20 (51.3)	6 (24)
Mod.	8 (18.6)	15 (32.6)	7 (17.9)	8 (32)
Severe	8 (18.6)	14 (30.4)	12 (30.8)	11 (44)
Total	43	46	39	25

Management

Immediate treatment consisted of draining the urinary tract through an indwelling urethral catheter and intravenous fluid therapy to correct hyponatraemia, dehydration and metabolic acidosis. Intravenous antibiotic therapy was commenced with at least two broad spectrum antibiotics, usually cefuroxime and metronidazole. Drainage was continued until a urine output of 2 to 3 ml/kg/h was established, acidosis corrected and urea and creatinine values were falling. Forty-eight to 72 h were usually required for this stage, during which time the upper urinary tract was examined by US. MCUG was then performed in the routine manner, though in the neonates this examination was usually carried out by manual expression with the baby anaesthetised in the operating theatre. The valves were then resected by endoscopic transurethral diathermy, passing the resectoscope through a perineal urethrostomy in all babies weighing less than 5 kg. Urethral catheter drainage was continued for 7 days post-operatively and oral feeding established with breast milk or humanised artificial milk (SMA, Wyeth Laboratories, Maidenhead). Appropriate quantities of 8.4% sodium bicarbonate solution were given orally to maintain a satisfactory plasma bicarbonate level and prophylactic antibiotic cover with a cephalosporin or cotrimoxazole was started. Occasionally, because of a rising plasma urea level, it was necessary to reduce protein intake to 1.5 g/kg body weight/24 h: the calorie deficiency was corrected with Caloreen. This alteration in diet was usually required for only 2 to 3 weeks. After removing the catheter, biochemical values were observed for a further week and, if remaining stable, the baby was discharged from hospital.

Subsequent follow-up comprised monthly visits to the out-patient clinic for full clinical and biochemical evaluation. Particular attention was paid to serum phosphate and ionised calcium levels in the babies with renal failure in an attempt to anticipate the onset of renal bone disease. When phosphate levels approached 2 mmol/l (6.2 mg/100 ml), a reduced phosphate diet was introduced with phosphate absorption inhibitors such as Aludrox (Wyeth Laboratories, Maidenhead) or calcium carbonate. Two babies developed complete feeding refusal and one of these (who was taking phosphate inhibitors) became severely hypophosphataemic. Eventually a period of tube feeding was required for both babies.

If progress was satisfactory, MCUG and IVU or renal US were performed 1 year after surgery. Subsequent investigations were regulated in accordance with the child's progress.

Surface Urinary Diversion Three children had cutaneous loop ureterostomies performed; one was unilateral following a contralateral nephrectomy. The ureterostomy was necessary because of obstruction following reimplantation of the ureter. Bilateral ureterostomy was performed in the other two children because of uncontrollable urinary infection and advancing renal failure. In both children a left nephrectomy was performed later because the kidneys failed to excrete urine; the right ureterostomies have been closed. If at the outset it had been appreciated that the left kidneys in these children were completely non-functioning, their removal would probably have averted the contralateral ureterostomies.

Nephrectomy Six kidneys were removed, five left and one right. With the exception of one left kidney all had reflux: the exception was a non-refluxing dysplastic kidney with a dilated ureter.

Results

Progress Following Initial Management

Ureteric Reflux Twenty-five children with reflux have been followed up for more than 1 year. In one of these the reflux (bilateral) appeared after surgery for the valves. There were 8 children with left reflux, 5 with right and 12 bilateral, providing a total of 37 refluxing ureters. Of these, 5 were treated by nephrectomy and 1 by cutaneous ureterostomy. Of the remaining 31 refluxing ureters, the reflux disappeared spontaneously in 10 (32.3%), was operated on in 19 and persisted in 2. This tendency for reflux to disappear without anti-reflux surgery has been noted by other authors (Cass and Stephens, 1974; Johnston, 1979; Egami and Smith, 1982; Hoover and Duckett, 1982). The author's policy was to perform anti-reflux surgery when the MCUG, 1 year after valve fulguration, demonstrated Grade 3 reflux (MRC Bacteriuria Committee, 1979) into a ureter whose kidney was deemed to be still functioning. More recently this policy has been changed inasmuch as operation is withheld unless the child is developing recurrent episodes of urinary infection.

Upper Urinary Tract Dilatation This was present radiographically or ultrasonographically in 43 children (96.5%), affecting the left side only in 5, the right side only in 2 and both sides in 36. Thirty-four children have been investigated post-operatively, producing 68 upper tracts for study. Of these, 6 were subjected to nephrectomy and 7 were undilated pre-operatively. Of the remaining 55 upper tracts, dilatation improved in 49, of which 22 were operated on, 17 for reflux. Dilatation did not improve in 7 upper tracts, 3 of which were treated by operation. Thus dilatation subsided spontaneously in 27 of 55 upper tracts (49%). This proportion might have been higher if the indications for anti-reflux surgery had been more strictly identified. Nevertheless, 33% of the upper tracts whose dilatation subsided spontaneously did have reflux. Of the non-refluxing upper tracts, ureteric reimplantation produced more obstruction in two ureters and little immediate change in the dilatation of the remainder. Improvement occurred more as a result of the passage of time than the effects of the operation.

Recovery of Renal Function Of the whole series, 13 children (28.3%) are now in renal failure. Thus of those whose renal function at diagnosis was depressed, 60.6% returned to normal. Three children have renal bone disease, 1 is hypertensive, 2 are on continuous ambulatory peritoneal dialysis (CAPD) and 1 has had a renal transplant. There were no deaths.

Two measurements, plasma creatinine and GFR, were studied to determine whether they were reliable in predicting the results of treatment in so far as renal function was concerned. Table 2 shows pre-operative and post-operative plasma creatinine values in 36 children. Of 18 children with moderate or severe elevation of plasma creatinine, 10 (55%) returned to normal. However, Table 3 shows pre-operative and post-operative values for GFR in 19 children. Of 15 children with moderate or severe depression of GFR only 4 (26.7%) recovered. Thus GFR was a more reliable method of predicting permanent renal failure.

Table 2 Posterior Urethral Valves. Pre- and Post-Operative Plasma Creatinine Values

Pre-operative			*Post-operative*		
			Normal	*Raised*	
				Moderate	*Severe*
Normal		18	17	1	0
Raised	Moderate	7	6	1	0
	Severe	11	4	2	5

Table 3 Posterior Urethral Valves. Pre- and Post-Operative GFR ml/min/1.73 m^2

Pre-Operative			*Post-operative*		
			Normal	*Depressed*	
				Moderate	*Severe*
Normal		4	4	0	0
Depressed	Moderate	5	3	1	1
	Severe	10	1	1	8

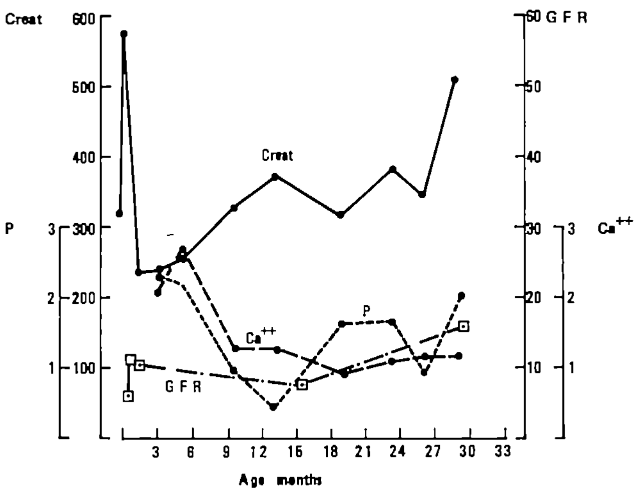

Fig. 3 Serum creatinine, ionised calcium, phosphate and GFR by age GFR was less than 10 ml/min1.73 m^2 at diagnosis. Severe hypophosphataemia as a result of dietary insufficiency occurred Subsequently renal bone disease developed. The child is now being treated by CAPD.

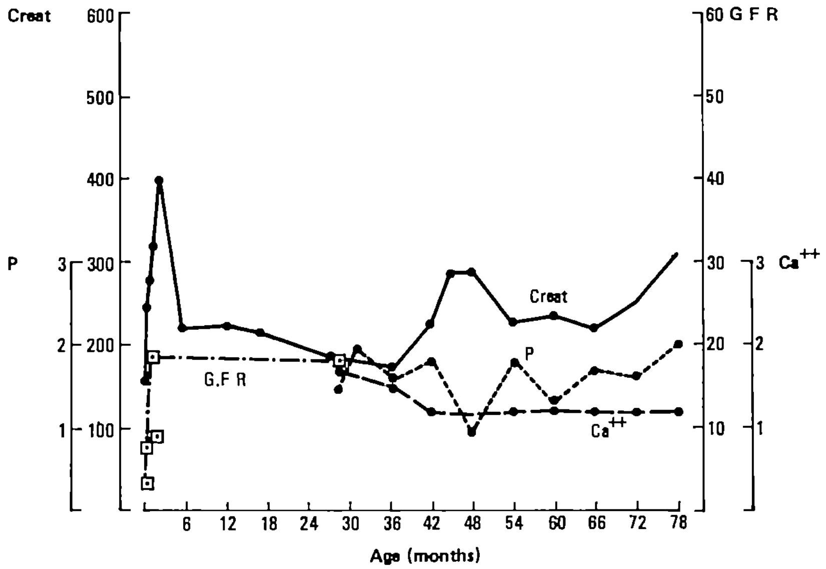

Fig. 4 As in Figure 3 This child also has renal bone disease Serum creatinine is beginning to rise steeply.

Two types of renal failure were seen, the immediate and the delayed. The first type affected neonates and young infants whose GFR at diagnosis was less than 50% of normal, *i.e.* 10 ml/min/1.73 m^2 or less. These children remained in renal failure (Figs 3 and 4) and it was necessary from the outset to take special care to prevent metabolic acidosis and hyperphosphataemia by providing appropriate quantities of oral 8.4% sodium bicarbonate solution and a low phosphate diet with phosphate inhibitors. Despite these measures, body growth soon became retarded and fell well below the third percentile (Fig. 5). Height and weight were equally affected. When evidence such as rising serum phosphate, falling serum ionised calcium and radiological changes at the epiphyses appeared, indicating the onset of renal bone disease, treatment with 1 α hydroxycholecalciferol was started and the dose regulated according to the serum ionised calcium levels. The onset of renal bone disease occured in two children with remarkable rapidity: one developed severe bowing of his tibiae and the other had pathological fractures of the humeri and femora.

The second type of renal failure occurred in children whose GFR at diagnosis was more than 50% but less than 75 to 80% of normal. In these children plasma creatinine levels remained at or just above the upper limit of normal and growth occurred initially at normal speed. However, in either early childhood (Fig. 6) or, more commonly, when the pubertal growth spurt began (Fig. 7), creatinine levels began to rise, probably because body growth velocity was exceeding renal growth velocity so that there was a fall in GFR proportional to body surface area.

Discussion

The high incidence of obstructive symptoms in the neonates but of infective symptoms in older infants and children suggests that the features of congenital urethral valvular obstruction are present from birth, are recognisable in the first month of life, but are frequently missed until infection precipitates an acute illness.

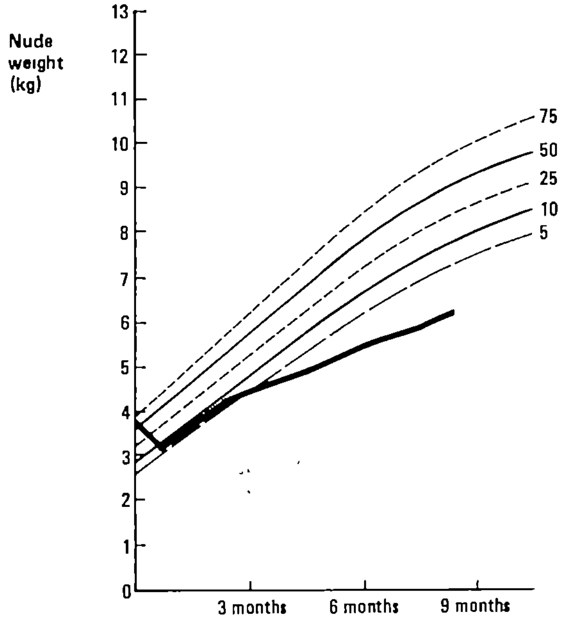

Fig. 5 Infants' body weight by age. Weight gain is falling below the third percentile.

Ureteric reflux in children with posterior urethral valves shows a marked tendency to disappear spontaneously, but in those ureters in which it fails to do so the kidney will, in many instances, be non-functioning and is best treated by nephroureterectomy. Anti-reflux surgery is indicated only in children in whom the kidney is still functioning, the reflux is Grade 3 and urinary infection is difficult to control. Renal parenchymal atrophy and scarring due to back-pressure and/or infection are initiated in the very early stages, mostly antenatally. Anti-reflux surgery will not influence their development. A greater contribution to renal salvage is likely to be made by antenatal US diagnosis and judicious early delivery of the fetus.

Dilatation subsided spontaneously in over half of the upper urinary tracts and nearly a third of these had reflux. The fact that the remaining two-thirds did not have reflux indicates that reimplantation of the ureter for non-refluxing dilatation is not necessary provided that the valves have been effectively treated. The dilatation will gradually subside spontaneously.

Depression of renal function, which was present in the majority of children, particularly when diagnosed under the age of 3 months, returned to normal in nearly two-thirds. The renal function test which most accurately predicted recovery from renal failure was the measurement of GFR. If, in a neonate, this was below 10 ml/min/1.73 m^2, recovery was unlikely and the need to commence a prolonged management programme for chronic renal failure was almost inevitable. Less severe renal failure did not usually impair childhood growth and development until the pubertal growth spurt was entered, when progressive chronic renal failure ensued.

The experience of this series suggests that children born with posterior urethral valves require treatment for the valves and little, if any, subsequent surgery. Provided the valves have been effectively destroyed, upper urinary tract dilatation will gradually improve and reflux will often disappear. Even if reflux does not disappear, anti-reflux surgery is not indicated unless the reflux is of gross degree, the kidney retains some function and recurrent urinary infection is proving difficult to control.

The main hope for lowering the incidence and reducing the severity of chronic renal failure is antenatal diagnosis and either intrauterine bladder drainage or early delivery of the fetus.

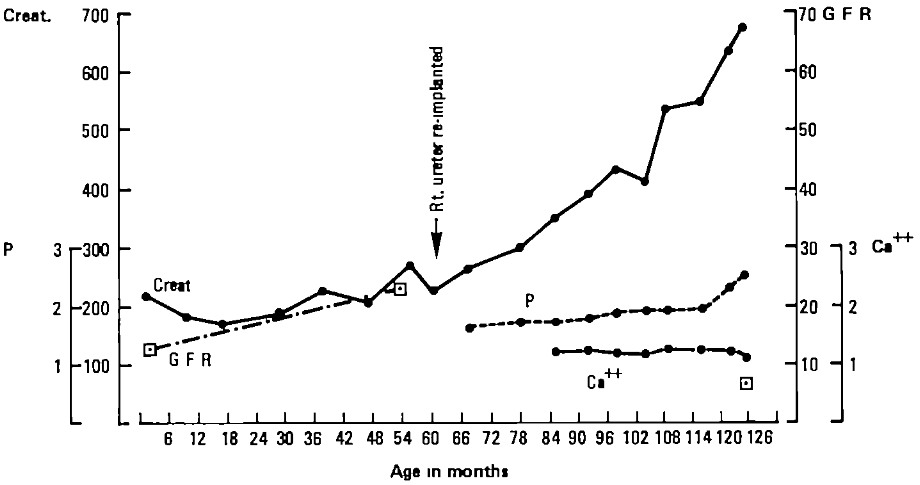

Fig. 6 As in Figure 3. GFR at diagnosis was between 50 and 75% of normal Serum creatinine remained between 150 and 200 μmol/l (1.7 and 2 3 mg/100 ml) until the age of 4 years, when a steady rise occurred.

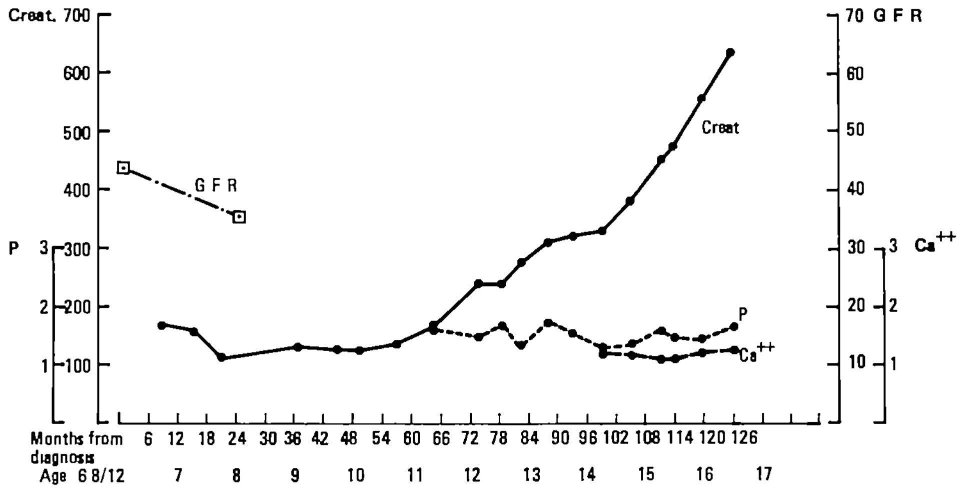

Fig. 7 As in Figure 3. Rise in serum creatinine level was coincident with pubertal growth spurt.

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The Author

J E. S Scott, FRCS, Senior Lecturer in Paediatric Surgery, Department of Surgery, University of Newcastle upon Tyne, The Medical School, Newcastle upon Tyne NE2 4HH

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Teflon Injection in Stress Incontinence

A. M. DEANE, P. ENGLISH, M. HEHIR, J. P. WILLIAMS and P. H. L. WORTH

St Peter's Hospitals, London

Summary—Forty-six patients, 28 females and 18 males, underwent periurethral or perurethral Teflon injection. The results in females were satisfactory, especially where resting anatomy was normal. Male results were disappointing, no patients with post-prostatectomy stress incontinence being cured.

Teflon or Polytef is pyrolysed polytetrafluoroethylene, the particles of which are encapsulated by a fibrous reaction enabling a permanent bolstering effect. It was initially used to bulk out the vocal cord in paralytic dysphonia (Arnold, 1963). The first major report on its use in stress incontinence appeared from the USA 10 years ago, Politano *et al.* (1974) describing periurethral injection in male and female stress incontinence with good to excellent results in 75% of 165 patients. They reported that some initial failures were due to poor case selection or inadequate volume injected. Although not always widely available, the popularity of the technique in Britain has been limited, although Lim *et al.* (1983) described cure in 21% or benefit in 54% of 28 females treated by periurethral injection. Endoscopic perurethral injection of Teflon was described by Heer (1977) and Lampante *et al.* (1979). Cure or great improvement was reported in 86% of 56 females by Schulman *et al.* (1983).

Patients and Methods

There were 28 females with stress incontinence and 18 males with post-prostatectomy sphincter damage. Synchronous video urodynamics (Bates *et al.*, 1970) were used to investigate the incontinence. Patients with unstable contractions were excluded, although a moderate degree of hypocompliance—up to an end filling pressure of 30 cm of water—was accepted.

Previous surgery had been performed in 10 of the 18 males (Kaufman procedure) and in 11 of the 28 females (colposuspension or anterior repair).

Female patients were classified as:

Grade I: Normal resting anatomy.
Bladder neck incompetence and descent on coughing.
Grade II: Bladder neck incompetence at rest.
Descent present but not below level of pubic symphysis.

More gross levels of descent (Grade III) were not considered for Teflon injection.

Cystoscopy was performed. In the male it is important to recognise any residual obstructing adenoma, which should be resected first. Polytef paste (Ethicon) was used, injected in the lithotomy positions by two methods:

(i) *Periurethral*

Female. A 17 gauge needle was inserted beside the urethra and advanced towards the bladder neck. Cystoscopic guidance checked the position and excluded bladder puncture or egress of Teflon. Three injections were performed at 3, 6 and 9 o'clock to produce submucosal cushions just below the bladder neck. Teflon is difficult to inject unless an insulin syringe is used. The effect on urethral closure can be observed endoscopically. Any Polytef which entered the bladder was washed out—a difficult task due to its tendency to stick to the mucosa.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Male. The needle was introduced transperineally towards the prostate apex, guided by a finger in the rectum. Two or more injections were performed in this region.

(ii) *Perurethral Endoscopic*

A Storz endoscopic needle was used via the catheterisation attachment. The urethra was punctured directly at 3, 6 and 9 o'clock and Teflon injected aided by a Storz metal piston syringe pump. In the female the injections were just below the bladder neck, in the male in the region of the distal sphincter. This technique seemed more accurate in the male, but not especially advantageous in the female. It was difficult to prevent some egress of Teflon from the needle track, requiring tiresome bladder washouts. In the male patients with gross membranous urethral scarring, the lumen could be difficult to puncture.

An average of 10 ml of Teflon was injected in each patient. The procedure was repeated in 60% of cases.

Results

Follow-up was for a minimum of 3 months and up to 2 years. Results were based on patients' subjective response.

Cure:	Entirely dry or only very occasional minor episodes of incontinence.
Improved:	Beneficially reduced episodes of incontinence.
Failed:	No significant improvement.

Females

Grade I—6 patients, 4 cured and 2 improved. No failures.

Grade II—22 patients, 5 cured and 6 improved. Eleven failures (50%), several of which were early cases and had undergone previous surgery. Some patients benefited from repeated injection.

Males

Periurethral—8 patients. The results were very poor, only one patient reporting improvement at 3 months. Remaining 7 were failures.

Endoscopic Perurethral—Initial results were encouraging, most patients leaving hospital with improved continence or even cure. To our disappointment most had relapsed at 3-month follow-up, although two reported some lasting improvement. Repeated injection did not seem to produce further improvement.

Complications No serious complications were seen, although pyrexia and transient voiding difficulties were common. If retention ensued, females were treated by intermittent self-catheterisation and males by suprapubic catheter.

Subsequent procedures were not jeopardised, but Teflonomas—fibrous encapsulated Teflon masses—required excision in males prior to a Kaufman procedure.

Discussion

Periurethral injection for female stress incontinence was first reported by Murless (1938), who injected sodium morrhuate around the urethra. The procedure, which gave reasonable results, was abandoned owing to an unacceptable incidence of pulmonary infarction attributed to embolism from the periurethral spaces. It has been shown in experimental animals that Teflon can embolise from the urethra (personal communication) and can even reach the brain. We have seen no complications as a result of embolism, but this product is still only licensed in the USA for use in the vocal cord and there must still be some minor reservations about its safety.

This study has established that control of stress incontinence can be obtained in the female, especially with only minor anatomical derangement. Gross bladder neck or trigonal descent would seem better suited to a suprapubic procedure. Detrusor instability is a relative contraindication, as in all procedures for stress incontinence.

We have been unable to repeat the good results claimed for the procedure in male post-prostatectomy incontinence. The patients referred were at least 1 year post-prostatectomy, when stress incontinence is usually irreversible except by surgical intervention. Several of the patients had membranous strictures, requiring prior urethrotomy, with gross scarring in the sphincteric region. The tissues could be almost cartilaginous, rendering periurethral injection difficult or impossible.

Despite reservations about its use in the male, Teflon injection provides a simple alternative for the control of early to moderate female stress incontinence.

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The Authors

A. M. Deane, FRCS, Urological Registrar, Norfolk & Norwich Hospital, Norwich.

P. English, FRCS, Research Registrar (Urology), Royal Infirmary, Manchester.

M. Hehir, FRCSI, Senior Urological Registrar, Jervis Street Hospital, Dublin.

J. P. Williams, MChir, FRCS, Consultant Urologist, St Peter's Hospitals, London

P. H. L. Worth, FRCS, Consultant Urologist, St Peter's Hospitals, London.

Requests for reprints to: A. M. Deane, Department of Urology, Norfolk & Norwich Hospital, Brunswick Road, Norwich, Norfolk NR1 3SR.

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AUTHORS' FOLLOW-UP

The Role of Internal Urethrotomy in the Prevention of Urethral Stricture following Transurethral Resection of Prostate

M. J. BAILEY and R. J. SHEARER

Department of Urology, St James' Hospital, London

Since our original report (Bailey and Shearer, 1979) we have continued to carry out routine internal Otis urethrotomy before transurethral resection of the prostate and have reviewed 882 consecutive patients. All were resected with the 27F Storz resectoscope. It is our policy to do a full-length urethrotomy in all patients but because of the sharp beak of the instrument no attempt is made to "force" it past the perineal membrane or prostatic urethra, and in 35 patients urethrotomy was done distal to the membrane only. Two of these patients (5.7%) developed membranous strictures.

The remaining 847 patients underwent full-length urethrotomy at 30F and 2 (0.24%) have developed a stricture, although the expected incidence would be 7 to 10% (55-85 patients). One of these two patients had a previous history of stricture and the other, who developed acute retention after hip replacement, had been catheterised with a 26F catheter—a practice no longer possible in this hospital.

During the same period 58 bladder neck incisions were performed using the 24F resectoscope. Initially no urethrotomy was done but 2 of 25 patients (8%) developed a stricture and we therefore now do a preliminary urethrotomy at 27F. None of the 33 patients so managed has developed a stricture.

There have been no major problems. Some bleeding from the prostatic part of the incision is evident but does not obscure vision and is easily controlled with diathermy if necessary. Some post-operative bleeding around the catheter is seen but soon stops spontaneously. In one patient this bleeding continued for about a day, but he had dramatic penile turgidity for 24 h after TUR and we attributed this to the anaesthetic. Two patients have commented on spraying of the stream, possibly due to altered anatomy at the external urethral meatus.

Otis urethrotomy is a reliable and safe method of avoiding stricture following TUR and as there seems no way of predicting which patients are at risk, we still recommend its routine practice.

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Requests for reprints to: R. J. Shearer, Department of Urology, St James' Hospital, Sarsfeld Road, London SW12 8HW

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Cytotoxicity of Latex Urinary Catheters

M. RUUTU, O. ALFTHAN, M. TALJA and L. C. ANDERSSON

Urological Unit, Second Department of Surgery and Department of Pathology, Helsinki University, Helsinki, Finland

Summary—After an epidemic of severe urethral strictures in cardiac surgery patients, all brands of latex catheters marketed in Finland were investigated for cellular toxicity with eluates made from the catheters. Four of the seven brands, including the one involved in the stricture cases, showed marked cytotoxicity and inhibited almost all cell growth in various human cell cultures when a 30% catheter eluate was used. DNA histograms of cells cultured with toxic catheter eluate showed inhibition of DNA synthesis. Silicone catheters did not influence cell growth, which correlates with the finding that no new stricture cases were seen after the latex catheters were replaced with silicone ones. Attention is paid to the facts that international standards regarding urethral catheter toxicity are lacking and that catheter quality control is insufficient.

Urologists usually regard post-catheterisation urethral strictures as the result of trauma during insertion of the catheter or of pressure necrosis of the urethral mucosa caused by a catheter lying *in situ* for a longer period. Such strictures are often found anteriorly at the meatus, the navicular fossa and the penoscrotal angle, and posteriorly at the membranous part and at the bladder neck (Devine, 1979).

Between 1980 and 1981 we observed a sharp increase in the number of urethral strictures in males who had undergone open-heart surgery and had had an indwelling catheter for a short period (Ruutu *et al.*, 1982). The strictures developed acutely with severe symptoms and usually involved the penile urethra, showing a string of pearls configuration (Fig. 1). In some cases the whole anterior urethra became a narrow rigid tube (Fig. 2) and thus differed from the usual post-catheterisation strictures (Ruutu *et al.*, 1984).

Similar strictures were reported by other authors (Smith and Neligan, 1982; Wesley-James, 1982; Sutherland *et al.*, 1983) and were also shown to occur after transurethral surgery (Syme, 1982).

Numerous complaints about latex catheters led to extensive investigations of these catheters in Australia. There was a good correlation between the cytotoxicity of some catheter brands and the complaints (Graham *et al.*, 1983).

Our stricture epidemic ceased when we abandoned latex catheters in favour of silicone ones. We decided to investigate urinary catheters to establish whether the strictures in our patients could have been caused by a toxic tissue effect.

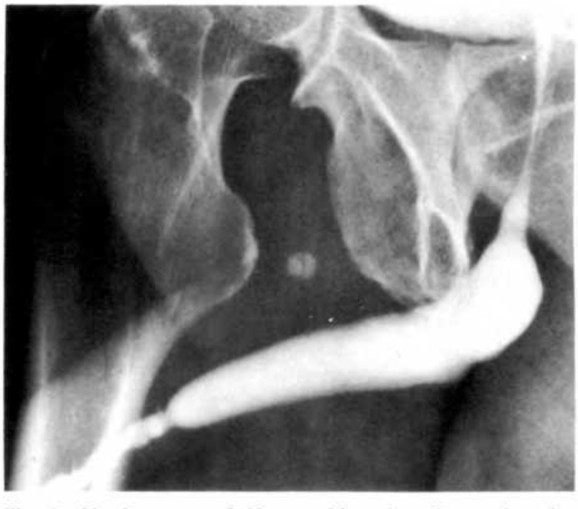

Fig. 1 Urethrogram of 49-year-old patient 5 months after coronary artery bypass grafting. Maximum urinary flow rate 5 ml/s.

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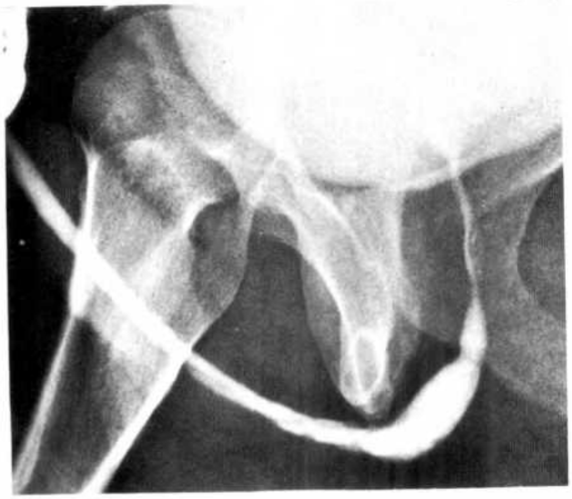

Fig. 2 Urethrogram of 30-year-old patient 3 months after reoperation for Fallot's tetralogy. Maximum urinary flow rate 4 ml/s.

Materials and Methods

Several catheters from all seven latex brands available on the Finnish market, as well as one plastic and two silicone brands, were investigated.

The catheters were cut into 2-cm lengths and eluted under sterile conditions in 100 ml RPMI-1640 culture medium at 37°C for 3 days. The eluate was then supplemented with 10% fetal calf serum and added at 0.1, 0.3, 1, 3, 10, 30 and 100% concentrations to cell cultures in microtitre plates. The culture medium without catheter eluate was used as a control. Six different continuous human cell lines were used: JM (T cell leukaemia), JOK-1 (hairy cell leukaemia), K-562 (erythroleukaemia), MDA-MB 231 (mammary carcinoma), SH-SY5Y (neuroblastoma) and U-937 (monocyte-macrophage cell line). After culturing for 48 h, cell proliferation was measured by adding 20 µCi ^{3}Htdr (tritiated thymidine) to each well 6 h before termination of the cultures. The CPM (counts per minute) value for each well was recorded. Triplicate determinations were done and the medians used as representative values. The results were expressed as percentages of the controls.

To find out whether the silicone surface on latex catheters labelled "siliconized", "coating contains silicone", "silicone treated", or "silicone bonded" could influence the results, another series of catheters was not cut into pieces but kept intact in the culture medium to yield a surface eluate.

DNA histogram. The cultured cells were washed twice with phosphate buffered saline (PBS). The cell pellet was resuspended in a buffer solution containing 50 µg/ml ethidium bromide (Sigma Chemical Co., St Louis, USA) in 0.3% Nonidet P40, 10 mM Tris and 2 mM EDTA. Quantitative fluorescence measurements were performed with a flow cytometer FACS IV (Becton and Dickinson).

Results

Most latex catheters showed some cytotoxic effect when a 100% eluate was used, but at lower concentrations there were marked differences.

Some catheters of brands 1 to 4 showed an almost total inhibition of all cell growth when a 30% eluate was used (Table). The same effect was seen whether these catheters were cut in pieces or a surface eluate was tested. Some catheters were especially toxic and inhibited almost all growth even with a 10% eluate.

Table The Effect of 30% Catheter Eluates on JM Cell Cultures

Brand	*Material*	*Pieces/ Intact*	*CPM % of control*
1	Latex (siliconised) Old formula	Intact	0.03
2	Latex (coating contains silicone)	Intact	0.06
3	Latex	Intact	0.06
4	Latex (silicone treated)	Intact	0.08
5	Latex (silicone bonded)	Intact	86.1
5	Latex (Teflon coated)	Intact	63.6
6	Latex (siliconised)	Pieces	82.6
7	Latex (silicone bonded)	Intact	67.7
8	Plastic	Pieces	75.5
9	Silicone elastomer	Pieces	98.0
2	Silicone elastomer	Pieces	71.9
1	Latex (siliconised) New formula	Pieces	72.4

All catheters of brand 2 were toxic. The toxicity of different dilutions of the eluate of such a catheter is seen in Figure 3.

There were marked differences between individual catheters of brands 1, 3 and 4. Even intra-batch variation was seen. Brand 1 catheters (involved in our stricture cases) were investigated according to the year of manufacture (Fig. 4). After recent reformulation of this brand the toxicity has been reduced (Fig. 5).

Brands 5 to 7 showed in general much less toxicity. Of these, brands 5 and 7 were Teflon coated or silicone bonded. A difference was seen in the cytotoxic effect of catheter pieces and intact catheters (Fig. 6).

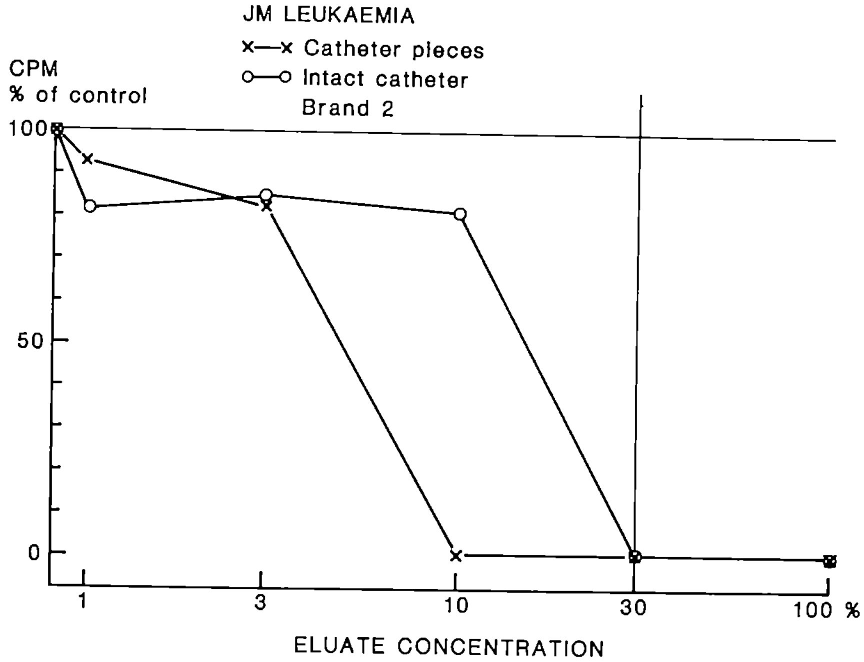

Fig. 3 Typical toxicity curves for brand 2 catheters. Almost total cell growth inhibition with 10, 30 and 100% eluate concentrations Logarithmic scale.

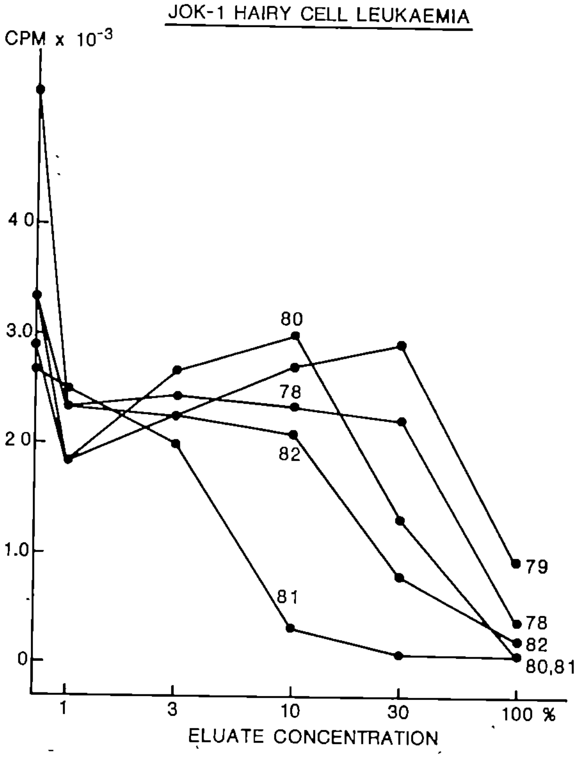

Fig. 4 Toxicity curves for catheters of brand 1 according to year of manufacture. Variation between toxicity at 10 and 30% concentrations

The full silicone catheters were non-toxic with all eluate concentrations. The plastic catheters inhibited ^{3}Htdr incorporation when a 100% eluate was used but were non-toxic with lower concentrations. The difference between a full silicone catheter and a non-toxic and toxic latex catheter is shown in Figure 7.

DNA histograms obtained from cells cultivated in the presence of toxic catheter eluate showed an inhibition of DNA synthesis and accumulation of cells in the S phase of the cell cycle when compared with the controls (Fig. 8).

Discussion

Cell culture tests have been used for biomedical screening for almost 20 years (Guess *et al.*, 1965; Rosenbluth *et al.*, 1965). They have, however, not been included in official standards for the testing of medical devices, which are based on various animal tests. International standards for catheter toxicity do not exist and most manufacturers rely on the rabbit muscle implantation test (US Pharmacopeia).

In the British Standards (1979), cell culture tests are recommended for cytotoxicity assessment of various medical devices, including urinary catheters, but the standards remain a recommendation

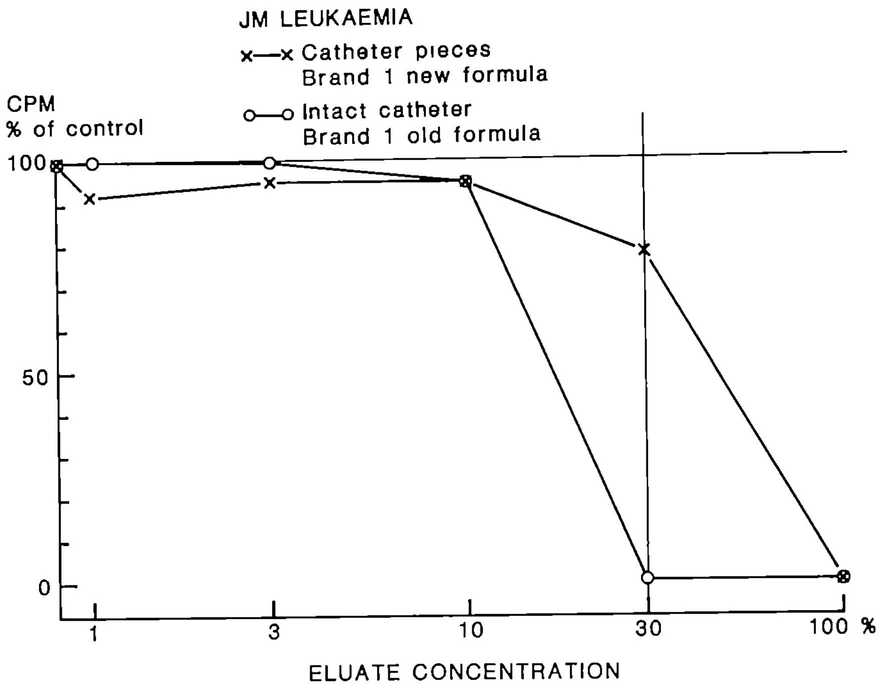

Fig. 5 Toxicity curves for an old and a reformulated catheter from brand 1

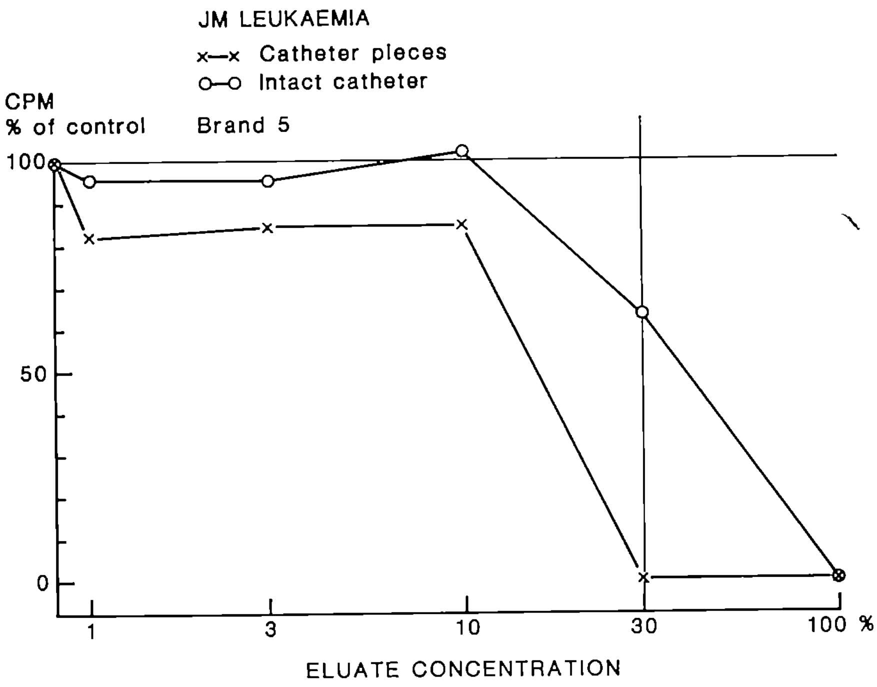

Fig. 6 Difference in toxicity of Teflon-coated brand 5 catheters from the same batch. The catheter pieces with the latex matrix exposed are considerably more toxic at 30% eluate concentration than the catheter with an intact Teflon surface.

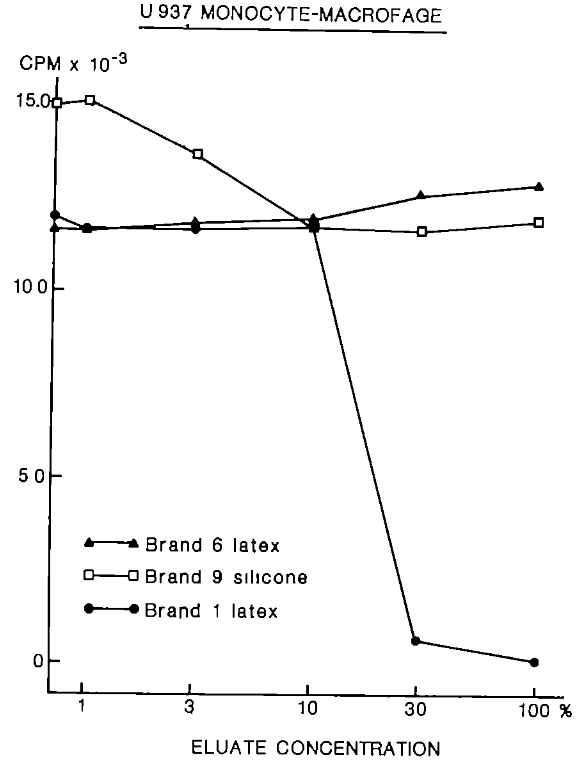

Fig. 7 The effect of various catheters on monocyte-macrophage cultures.

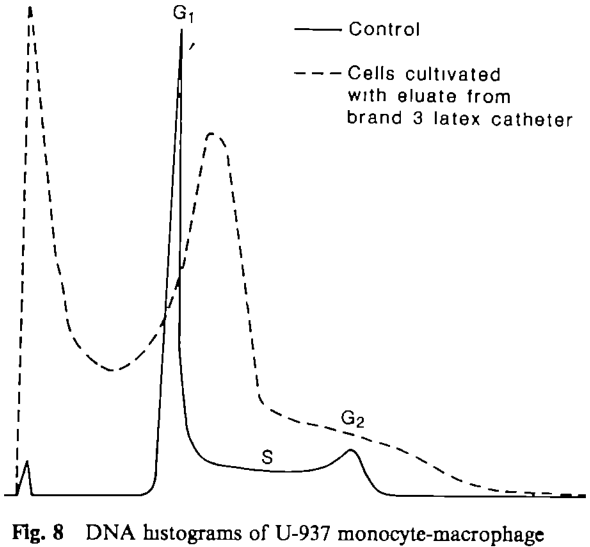

Fig. 8 DNA histograms of U-937 monocyte-macrophage cells with and without toxic catheter eluate.

as long as generally accepted limits for toxicity are not established. The cell culture tests are known to be sensitive, but the policy of discarding medical devices tested only with such tests has been criticised because a correlation between *in vitro* toxicity to cells and clinical adverse effects has not been documented properly (Engel, 1983). Our cell culture test was reproducible. It was also quantitative because the results could be expressed in exact figures. This is an advantage when compared with different animal implantation tests which are qualitative. The rabbit muscle implantation test was carried out simultaneously with the cell culture test. The results from both assays correlated well, but the cell culture test was more sensitive. The Australian group came to the same conclusion using a slightly different method (Graham *et al.*, 1983). Personal communication with the authors revealed that the same four catheter brands showed the highest toxicity in both culture methods.

The panel of cell lines used in this study represents different phenotypes. The epithelial mammary carcinoma cell line MD-MBA 231 and the neuroblastoma cell line SHSY-54 grow adherent to the surface, while the haematopoietic cell lines grow in single cell suspension cultures. Results from the toxicity studies obtained with the different cell lines were consistent throughout. There was only a slight difference in the relative sensitivities, which could be explained by the variations in growth rate (replication times) between the different lines.

A cell line derived from normal urethral epithelium was not available, but since the transitional cell epithelium is continuously renewing *in vivo* there is no reason why the proliferating basal cells should not be sensitive in a similar way to toxic substances in the catheters.

In recent experimental work the effect of various catheters on the rat urethra was examined histologically. Silicone caused only mild oedema, while latex caused moderate inflammatory infiltrate, epithelial loss and some haemorrhage (Edwards *et al.*, 1983). This *in vivo* finding is in accord with the various cell culture results. Wilksch *et al.* (1983) compared subcutaneous implantation of catheter pieces into rats with the cytotoxic effect of soluble extracts from catheters on cultured macrophages. The results correlated well.

Most stricture outbreaks have involved cardiac surgery patients, but the role of extracorporeal perfusion remains unknown. We have occasionally seen patients with similar strictures after major abdominal surgery, but in those cases the catheter material and brand were unfortunately not noted by the surgeon. Syme (1982) reported a stricture rate of 36% among patients with transurethral prostatic surgery. The catheter brand implicated was the same as in our cardiac surgery patients (personal communication). Thus the complication is not restricted to patients with extracorporeal perfusion. Poor documentation of the catheter brands used and reluctance to report occasional strictures create major problems in the registration of urethral complications associated with catheters.

In the manufacturing process of urinary catheters much attention is paid to good mechanical properties. To make the surface smooth for insertion, most latex catheters are coated with a thin layer of silicone. According to industrial information this layer, however, can melt away after a few hours in the urethra and the urethral epithelium is then exposed to direct contact with the latex. This explains why the various labels "siliconised", "coating contains silicone" or "silicone treated" did not protect against cytotoxicity when the catheters were kept intact in the culture medium. The Teflon-coated and silicone-bonded catheters were better in this respect.

Latex comes from different plantations in tropical countries and in the manufacturing process several chemicals are used. The exact formulas are unknown to us because of the reluctance of the manufacturers to release them—unlike pharmaceuticals, the composition of medical devices can be kept secret.

The manufacturers use various animal tests in their product quality control. The rabbit muscle implantation test is generally regarded as the principal screening method. However, the catheters which were highly toxic according to our cell culture method failed the rabbit muscle implantation test too. This finding arouses the suspicion that biomedical quality screening is carried out too infrequently. In two cases we were told that the mice systemic toxicity test (US Pharmacopeia) was mostly used. This test has been shown to be greatly inferior in sensitivity when compared with rabbit muscle implantation or cell cultures (Graham *et al.*, 1983) and should be abandoned.

In our opinion there is now considerable evidence of the cytotoxicity of latex catheters and all medical personnel should be aware that adverse urethral reactions in connection with catheterisation can be induced both chemically and mechanically. Urologists should advise hospital staff to switch to silicone or plastic catheters despite their higher cost until better quality control of latex catheters has been established.

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The Authors

M. Ruutu, MD, Research Fellow, Urological Unit, Second Department of Surgery
O Alfthan, MD, Associate Professor of Urology
M Talja, MD, Registrar in Urology
L C Andersson, MD, Professor of Pathology

Requests for reprints to: M Ruutu, Rauduntie 13 E, 02130 Espoo 13, Finland

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Potential Use of Ultrasound in Place of X-ray Fluoroscopy in Urodynamics*

M. C. BROWN, J. R. SUTHERST, A. MURRAY and D. H. RICHMOND

Bioengineering and Medical Physics Unit and Department of Obstetrics and Gynaecology, University of Liverpool, Liverpool

Summary—A moving picture can be obtained using an ultrasonic scanning probe in the rectum to provide information about the bladder and urethra in the same projection as for lateral cystography. The method has potential as a substitute for cinecystography but there are a number of problems still to be overcome.

The bladder base can be viewed by ultrasound through the full bladder with a transducer on the skin just above the pubis (Ostergard, personal communication). A range of ultrasound probes is also made for viewing the prostate gland from the rectum. However, the best view of the bladder base can be obtained with a linear-array real-time scanning transducer placed in the rectum, as described by Nishizawa *et al.* (1982). This provides a sagittal section of the bladder base which includes the urethral internal meatus. Nishizawa *et al.* described how the system may be used to replace the X-ray cystography element of a conventional urodynamic imaging system. Other work using the same technique has been presented by Perkash and Friedland (1983) on viewing the bladder base and proximal urethra in males with spinal injuries. We have begun evaluating the system for studies of bladder base dynamics, particularly for the investigation of women with urinary incontinence (Brown *et al.*, 1983).

The machine used was a Toshiba SAL-30A ultrasound scanner with a matching linear-array rectal probe, although several manufacturers now offer such a probe with their real-time scanners. The active part of the probe is covered by a condom, and after insertion into the rectum, water is passed into this sheath from a syringe. The ultrasound picture of the bladder base now appears on the screen and the probe is rotated until it scans postero-anteriorly. In our tests we then introduced a 12F urethral catheter to identify the internal urethral meatus. The output of the scanner is in video format which can be mixed with the urodynamic pressure records for simultaneous presentation.

The form of image is as shown in Figures 1 and 2, in which anatomical features (such as the cystocele in Figure 2) can be seen easily. We have been particularly interested in movement of the bladder base during stress (cough) and the effect on the urethrovesical junction, especially when a urethral catheter is present.

During stress we have observed that there may be (a) movement of the bladder base, (b) movement of the urethrovesical junction, which may not always be in the same direction, (c) change in the angle of the urethra which can be determined from the flexion of the catheter as visualised in Figure 1, and (d) apparent movement of the catheter with respect to the urethra. Figure 2 shows that the urethral catheter protruded into the bladder by about 2 mm but disappeared during coughing.

By withdrawing the catheter slowly we were also able to relate the observed urethrovesical junction to the urethral closure pressure profile (UCPP). All of these observations are easier to review from the video records than from still pictures.

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* Based on a presentation made at the Thirteenth Annual Meeting of the International Continence Society held at Aachen, Federal Republic of Germany in 1983.

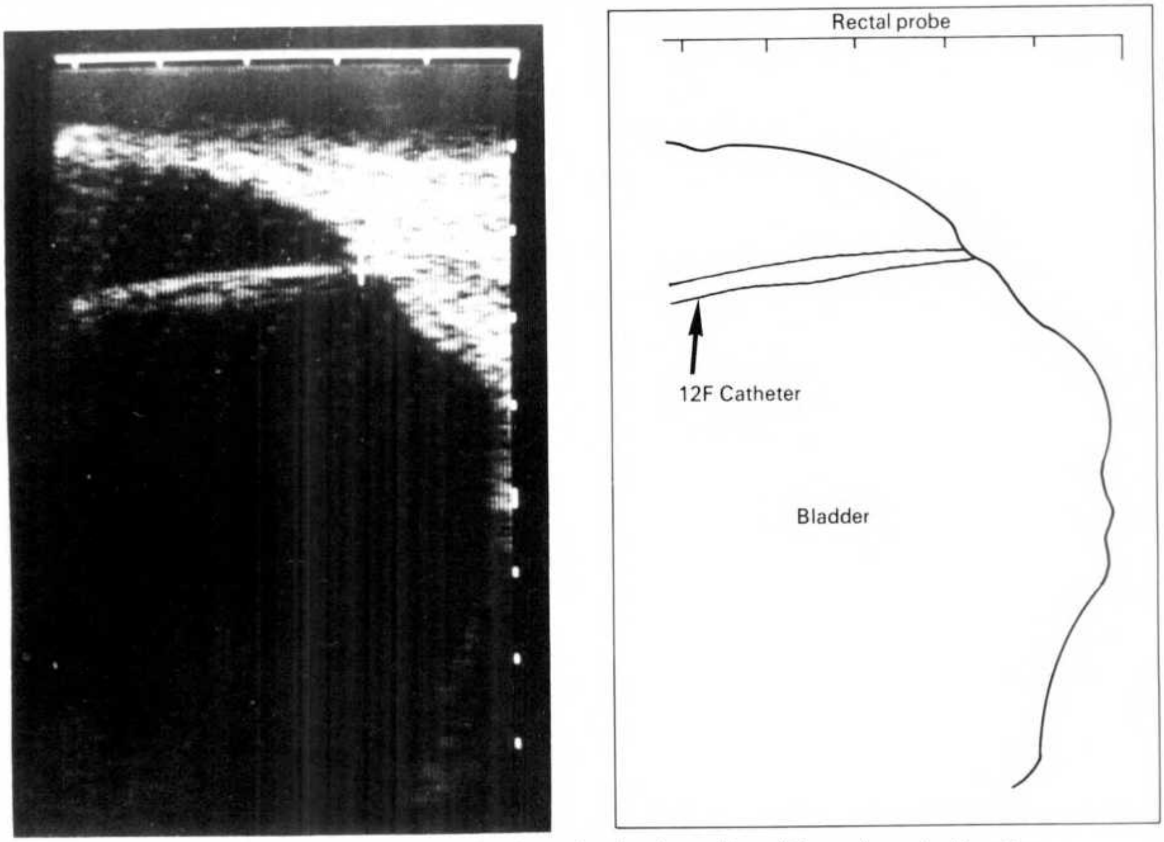

Fig. 1 Bladder base and 12F urethral catheter showing the position of the urethrovesical junction.

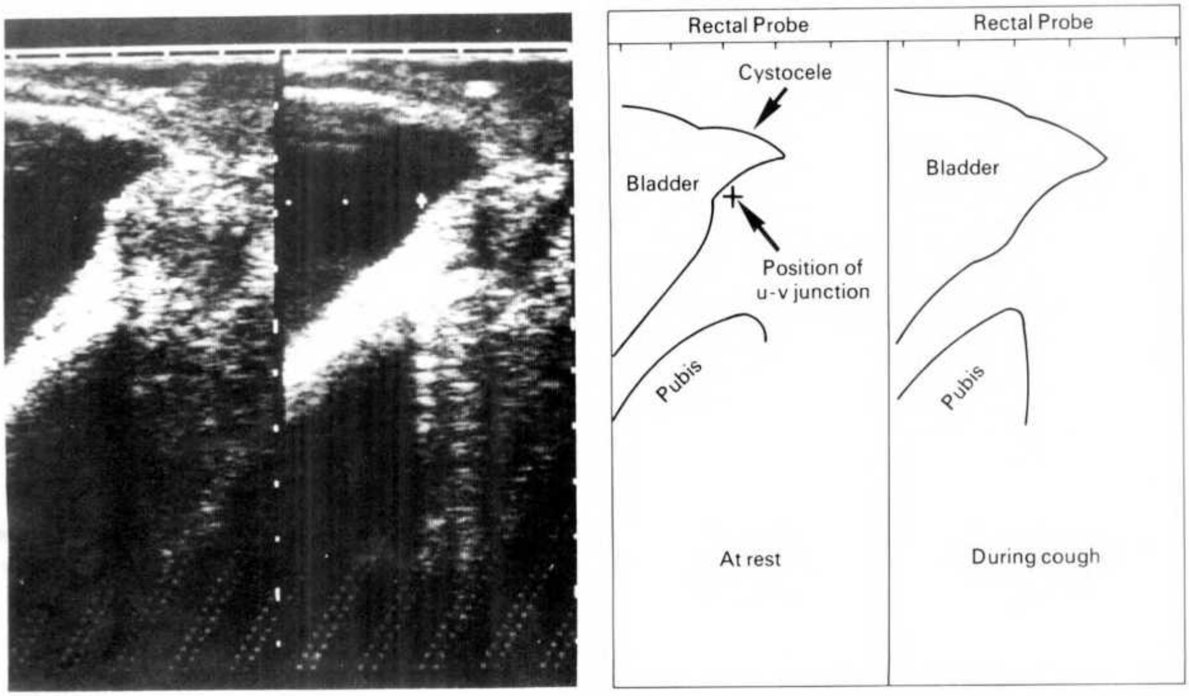

Fig. 2 Cystocele seen before and during cough.

The technique clearly needs further development. The probe is rather large and could be preventing free movement of the bladder. A second problem is that the probe itself moves during stress, giving a false impression of motion, and thus the distortions reported as occurring during stress by Perkash and Friedland (1983) may be partially of artefactual origin. It is not immediately obvious where the probe should be fixed. The catheters we had were not very reliable markers and disappeared from view at some orientations. There were also a number of artefacts (possibly due to reverberation) which demanded some patience during interpretation.

Despite these difficulties, there is clearly considerable potential for the use of ultrasound in view of its relative safety, ease of use and cost.

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The Authors

M C. Brown, BSc(Eng), PhD, Principal Physicist, Royal Liverpool Hospital

J. R Sutherst, MD, FRCOG, Reader in Obstetrics and Gynaecology, University of Liverpool.

A Murray, MRCOG, Consultant Obstetrician and Gynaecologist, Arrowe Park Hospital, Wirral.

D H Richmond, MRCOG, Lecturer in Obstetrics and Gynaecology, University of Liverpool

Requests for reprints to M. C. Brown, Bioengineering and Medical Physics Unit, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP

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Abstracts of the Proceedings of the Urological Society of Australasia, 37th Annual General Meeting, Melbourne, Australia, 1984

President: D. Lenaghan
Secretary: R. D. Wines
Editor: J. P. Maddern

The 37th Annual General Meeting of the Urological Society of Australasia was held in Melbourne from 1-5 April. The principal guests at the Scientific Meeting were Dr J. P. Donohue from Indianapolis and Dr J. Grayhack from Chicago, Professor R. Hohenfellner from Mainz and Drs V. J. O'Connor and E. A. Tanagho from the United States also contributed to the programme. Dr S. Simhombing from Bandung, Indonesia, and Dr R. L. Lo from Hong Kong were other welcome contributors. The immediate Past President of the Royal Australasian College of Surgeons, Mr J. K. Clareborough, delivered the Harry Harris Oration, choosing as his subject "Behind the Looking Glass".

The Keith Kirkland Prize, awarded for the best presentation of a paper by a trainee, was awarded jointly to Dr D. R. Eisenger of Sydney and Dr L. Thompson from Brisbane.

Neoplasia

Renal Cell Carcinoma: Indicators of Prognosis

By J. N. Nacey and B. Delahunt
Departments of Urology and Pathology, Wellington Hospital, Wellington, New Zealand

A retrospective analysis was carried out on 162 patients presenting to Wellington Hospital with renal cell carcinoma between 1958 and 1978, to evaluate clinical and pathological factors that may influence prognosis

Staging, following radical nephrectomy, was performed using Robson's classification with a 5-year survival rate of 70% for stages 1 and 2, 53% for 3A, 13% for 3B and 3C and 0% for stage 4 disease. This illustrates the very strong predictive value of survival using this staging method. Patients with renal vein or caval involvement (stage 3A) had a significantly poorer survival rate than those with stage 1 or 2 disease, and significantly improved survival over those with nodal involvement. The highest attrition occurred during the first year and once the 3-year period was reached the survival rate following nephrectomy was similar to that of an age-matched non-cancer population.

The patients presenting with the renal cancer as an incidental finding had a survival rate similar to those with stage 1 disease and have a significantly improved outlook over any other mode of presentation. Those presenting with anaemia, weight loss, and metastases had very similar poor prognoses. By definition, those with metastases are stage 4 and by stage alone carry a poor prognosis, as do those with weight loss However, nearly half of those with anaemia were grouped in stages 1 to 3 and one would have expected these patients, on the basis of stage, to have a much better survival than shown. Patients with a peripheral lymphocyte count of $>2000\ \text{mm}^3$ showed significantly longer survival than those with lymphocyte counts below this level. The ESR had no bearing on survival.

Predominantly clear cell tumours were the most common, and this cell type offered a better prognosis than tumours with a granular cell pattern. No patient with spindle cells survived beyond 3 years Medium and high grade nuclear pleomorphism, and tumours with a mitotic rate of >5 when counted over 50 high power fields were all associated with a poor prognosis.

Renal Lymphoma—Another Space Occupying Lesion?

By R. D. Wines
Royal Prince Alfred Hospital, Sydney, New South Wales

This report described the pathogenesis of radiological changes which can be seen with renal involvement in lymphoma A study was made of the renal involvement of 82 patients dying from lymphoma. The findings were.

(i) The kidney is at least microscopically involved in 25% of patients with lymphoma, occurring least often in Hodgkin's disease.
(ii) The renal involvement is generally not of clinical significance
(iii) Ultrasonically, multiple large lymphomatous nodules in the kidney can be confused with polycystic disease.
(iv) Any single large intra-renal mass should be investigated and managed as if lymphoma was not present.

Radical Prostatectomy—Technical Problems

By R. B. Brown

Alfred Hospital, Melbourne, Victoria

A series of 24 patients with clinical B1 prostatic carcinomas who underwent radical retropubic prostatectomy and were followed for a minimum of 5 years was presented. Early complications included bleeding (17%), post-catheter withdrawal urinary wound drainage (20%) and large bowel trauma (4%) Late complications included impotence (100%), incontinence (65%), bladder neck stenosis (8%) and death from metastatic prostatic carcinoma (4%) There has been no evidence of local recurrence of the neoplasm in any of the patients so far. The ideal of removing the prostate gland and all of its lymphatic drainage is not achievable, whilst the operation, in the author's hands, has often proven to be difficult to perform, particularly in obese patients.

Specific points discussed to reduce the incidence of complications included pre-operative large bowel cleansing, hypotensive anaesthesia, a supine operating table position with a 20° Trendelenberg tilt, a flexed table and a sacral support. Additional technical points were the use of a vertical midline incision, particularly if the patient was obese, incising the endopelvic fascia at the most optimum point which allows for the creation of a posterior tunnel between the prostate, membranous urethra and the rectum but still remains just lateral to the anatomical prostatic capsule and early ligation of both the dorsal venous plexus and the anterior and lateral peri-prostatic and peri-bladder outlet vessels. The patients who were continent after the operation were those in whom it was possible to retain at least a portion of the bladder neck without compromising a radical clearance of the prostate gland, whilst those patients with severe incontinence were those in whom it was necessary to remove all of the bladder neck

The incidence of impotence in this small series is higher than that published by other urologists and this may have resulted from excessive apical and related area trauma and/or to excessive lateral dissection.

Transrectal Prostatic Ultrasound—Its Place and Application

By P. J. Metzner

St Vincent's Hospital, Melbourne

Carcinoma of the prostate is usually of insidious onset, is frequently slow growing and yet it is dynamically progressive. Prostatic neoplasia most usually presents at an advanced stage when cure is not possible but if detected early, then surgery or megavoltage radiotherapy can allow for a normal tumour-free life expectancy, *i.e.* a cure. Mortality from carcinoma of the prostate progresses with the stage at detection, so the earlier the tumour is detected the better the chance for patient cure. Patients with Stage A tumours are most frequently detected because of conditions other than neoplasia, *e.g.* benign prostatic hyperplasia. Stage B tumours usually rely on clinical acumen and it is in the detection of these tumours that transrectal ultrasound is invaluable in the assessment of the prostate.

Transrectal prostatic ultrasound will allow for accurate sizing of a gland, will demonstrate the capsule and its integrity and will give a characteristic echogenic pattern to determine benign prostatic hyperplasia, stones, tumour or inflammation. A scan will also be of importance to assess Stage A carcinomas that are not being treated but watched and to monitor the effects of hormones and X-ray therapy for Stages B, C and D. It will also give early warning of the resurgence of tumour growth following treatment.

A screening programme has been developed to assess men over 50 years of age to monitor their prostates and to determine changes that might indicate the presence of tumour and the need for specialist assessment. The backup for this programme is a computer based registry that will respond to a rating bestowed on the patient by the assessing radiologist and this registry will initiate review on a regular basis. It will also inform the general practitioner and reinforce an educational programme designed to help both the practitioner and patient once that patient is entered into the registry.

This programme has gained both patient and practitioner acceptance and seems to fill the need in preventative medicine to allow for early detection of a prostatic tumour and to provide the urologist the best possible chance of treating the tumour at an early stage. It is providing an increased state of awareness in the medical community and the population at large of the prevalence of this tumour and of the effectiveness of treatment in the early stage.

The Control of the Primary Prostatic Tumour Area by Titrated Dose Irradiation

By A. M. Jelliffe and Turner-Warwick

Middlesex Hospital, London, UK

Only a proportion of prostatic tumours respond to hormonal manipulation. This is the basis of the treatment of metastatic disease but it is unacceptably unreliable for the control of the primary tumour area. Thus the treatment of the primary area of a prostatic carcinoma and the control of metastases are distinct entities requiring separate decisions.

Failure to control the local disease is not reflected in survival statistics, nor is it commonly reported, but it compromises the quality of the patient's life because of:

(i) Re-enlargement of the prostatic remnants with recurrent bladder outflow obstruction.
(ii) Tumour invasion of the distal sphincter mechanism and impaired urinary control
(iii) Fungating intravesical tumour with haematuria and lower ureteric obstruction.

Thus with the exception of the few that are resolvable by local surgery, primary prostatic tumours are routinely irradiated almost irrespective of the age of the patient or the extent of the disease.

The complications of conventional irradiation treatment of the primary tumour area, proctitis, contracted bladder, sphincter damage, urethral stricture and impotence, can be virtually eliminated by the accurate use of small fields and by titrating the depth dose according to local tissue reaction—curtailing the course at the onset of significant rectal symptoms

The effective control of the local tumour is indicated by a halt in its progress rather than regression. It is evaluated by rectal palpation, ultrasound and persistence of efficient voiding with good control. This tumour control is often maintained indefinitely in spite of the fact that needle biopsies are positive in more than a third of the cases over many years and this suggests that one important effect of irradiation, both conventional and titrated, is to revert aggressive tumour behaviour to the biological latency which is a natural characteristic of many prostatic tumours.

Treatment is planned using three fields to cover an appropriate volume, commonly a 10 cm cylinder aiming at a depth dose of 5000 to 5500 cGy in 5 to 6 weeks but curtailing the treatment shortly after the onset of significant rectal symptoms. The incidence of persistent irradiation complications has been virtually eliminated in our series of more than 150 cases over the past 18 years but local control does not appear to have been significantly reduced in those in whom the dose had to be reduced to the region of 4500 to 4800 by local tissue response

Selection of Patients for Curative Therapy of Prostatic Cancer

By L. K. Cleeve

Repatriation General Hospital, Heidelberg, Victoria

In the absence of a method for curative treatment for generalised disease, we must focus on the group of patients with carcinoma of the prostate whose disease is localised, and therefore potentially curable by total prostatectomy.

At the Repatriation General Hospital, Heidelberg, 55 of 429 patients (12.5%) were accepted for total prostatectomy This report attempts to identify and perhaps expand this group.

Younger, fit patients with biopsy proven disease localised to the prostate, with no evidence of dissemination or nodal spread are the ideal candidates for cure.

The assessment of local disease is plagued by understaging. CT scanning has not been helpful but rectal ultrasound is a promising tool. T1 and T2 as well as selected T0 and early T3 tumours are suitable for cure. Grading and Gleason numbering provide information about the biological potential of individual tumours Bone scan is a sensitive method of detecting bony metastases Acid phosphatase elevation, even in the absence of detectable dissemination, clearly carries a poorer prognosis.

Nodal involvement is, in the early stages, clinically silent. Detection of positive nodes by CT scan and/or lymphangiography has been disappointing, although skinny needle aspiration of dubious nodes has helped. Pelvic node dissection may be the final arbiter but lacks therapeutic justification for such invasive staging. It is clear, however, that silent nodal involvement is present in 25 to 30% of those with T2 disease.

Expansion on clinical grounds only of this small but curable group of patients will increase the incidence of treatment failure.

Red Cell Surface Antigens in Bladder Tumours

By S. J. Clarke and J. B. Hall

Departments of Urology and Histopathology,
Repatriation General Hospital, Heidelberg, Victoria

Specific red cell adherence (SRCA) testing has been shown to be of some prognostic value in bladder tumours. The test has not been generally adopted, however, as it is crude and time-consuming. A different technique was used to assess the presence of ABO antigens, and compared the results to histological grade.

Paraffin blocks of first bladder tumours presenting in 1977 and 1978 were resectioned. The tissue was processed using an immunoperoxidase technique and monoclonal antisera to the A, B and O (H) antigens.

There was a spectrum of results, from almost complete retention of antigen to substantial loss. Previous investigators have reported the SRCA test as simply positive or negative, but we found intermediate degrees in intensity of staining and in distribution within the specimen We believe that the results should be seen as part of a continuum, in the same way as tumour grade.

In 17 group A patients there was very good correlation of test results with the patient's ultimate survival Good correlation was not observed in 4 group B patients. Similarly, the monoclonal anti-H antiserum, never previously applied to this situation, produced a poor correlation in 17 patients.

To compare prognostic accuracy with histological grade the assumption was made that patients with antigens strongly present should survive, whilst those with substantial loss of antigen would perish On this basis the test correctly predicted the outcome in 55% of cases, compared with 68% when similar assumptions were applied to tumour grade. In group A patients considered separately the rate was 73%

In this study using stored tissue, the test was not as accurate a prognosticator as grade, but could be expected to improve when used with fresh tissue. Monoclonal anti-H antisera with slightly different specificities might also perform better

Surveillance Alone in Clinical Stage I Non-seminomatous Germ Cell Tumour of the Testis (NSGCT)

By R. K. Lo, E. Johnson, C. von Eschenbach and D. A. Swanson

M. D. Anderson Hospital, Houston, Texas, and Hong Kong

The combined use of lymphography, computed tomography and determination of serum tumour markers has markedly improved the staging accuracy for Stage I non-seminomatous germ cell tumours of the testis, with the failures occurring in patients with microscopic disease undetectable by studies available at this time In pathological Stage I patients, relapses occur in sites other than the retroperitoneum. Platinum-based combination chemotherapy salvages over 90% of these patients. Accordingly, given the known morbidity and complication rate, the routine use of retroperitoneal lymphadenectomy or radiation therapy appears to be unjustified.

To test this hypothesis, 31 consecutive patients with clinical Stage I NSGCT were entered into a programme of orchiectomy followed by metastatic studies every 2 to 3 months With a median follow-up of 18 months, 25 have remained free of disease. Six patients have relapsed, all within the first 6 months. The sites of metastases were the lungs in 3, the retroperitoneum in 3 patients; in one patient the only evidence of metastasis initially was an elevation in tumour markers. The majority of the patients have therefore been spared the morbidity and resultant infertility of a retroperitoneal lymphadenectomy.

Other methods to determine the risks of relapse such as the primary tumour extent, and serum tumour marker decay pattern analysis, are also presented

In a controlled setting, a surveillance programme for patients with clinical Stage I NSGCT is feasible, justified and cost-effective.

Problems with Drug Therapy in Testis Tumours

By W. I. Burns

St Vincent's Hospital, Melbourne, Victoria

Toxicity data were presented from the Australasian Germ Cell Neoplasm Trial which accrued 239 evaluable patients from over 20 centres in Australia and New Zealand between 1979 and 1983 Generally speaking, the toxicity was acceptable but some toxicities, especially pulmonary, were disturbing and hopefully can be reduced in the future

Gastrointestinal Toxicity Nausea and vomiting were very common (95%), but generally this was short-lived and only 4 patients stopped treatment because of this side effect. However, 40% of patients who achieved complete remissions refused randomisation to the maintenance phase of this study, mainly due to anticipated gastrointestinal side effects of ongoing treatment. Trivial or mild diarrhoea occurred in 24% of patients.

Leukopenia and Neutropenia Severe leukopenia and neutropenia were frequent, especially in patients who had had prior irradiation or prior chemotherapy with agents not included in this study. Serious infection, however, was infrequent, with 12% having debilitating or grade III infection and 5% having life threatening infection (4 patients died from septicaemia). Two of these patients were in complete remission at the time. There was one death due to a bleeding peptic ulcer which was almost certainly coincidental.

Neurological Toxicity This was mainly peripheral neuritis due to the combined effects of cis-platin and vinblastine and was trivial to mild in 31% of patients Two per cent were recorded as having moderate to severe weakness of ileus for more than 5 days. Peripheral neuritis was probably under-reported and it is noted that resolution can be quite delayed and interfere with rehabilitation of patients cured of their tumour. Deafness that was clinically significant occurred in only 3% of patients. However, two patients had their treatment discontinued because of this and it is felt that that action was inappropriate.

Renal Toxicity This was less than anticipated and probably reflects the care taken with hydration and the monitoring of renal function Three per cent of patients developed creatinine levels greater than 0.4 and all were associated with septicaemia. Because of the synergistic toxicity of aminoglycoside antibiotics following cis-platin chemotherapy, beta lactam group antibiotics would be an appropriate safer alternative. Hypomagnesaemia is probably quite common but magnesium levels were not routinely measured in the study. Hypomagnesaemia causing weakness was noted in some patients and this side effect can persist for long periods, although it is easily treated with oral magnesium supplements.

Pulmonary Toxicity The incidence of this was higher than expected, possibly due to the impaired excretion of bleomycin due to transient impaired renal function from cis-platin. There were 7 deaths from pulmonary toxicity and 6 of these patients were in complete remission at the time. The greatest risk was associated with anaesthesia at a time when residual masses were being resected from the chest or abdomen after incomplete resolution on the chemotherapy. Anaesthesia should be given without added oxygen due to the increased sensitivity of the lung to oxygen following bleomycin therapy. This effect can last up to 12 months after bleomycin therapy has been completed and all patients should be warned about this problem, so that if they require an anaesthetic for any reason the anaesthetist can be warned.

Chronic Toxicity Long-term toxicity has not been a problem in this trial; second malignancies such as acute leukaemias seen after radiation and chemotherapy for Hodgkin's disease have not been encountered. Infertility is frequent even prior to chemotherapy but this side effect appears to be partially reversible. A recent report has found 75% of patients had some return of fertility within 18 months of chemotherapy.

Squamous Cell Carcinoma of the Urethra

By E. G. Holmes
Royal Brisbane Hospital, Brisbane, Queensland

A review of primary squamous cell carcinoma of the urethra in Queensland revealed five male cases in the years 1970 to 1983

A review of the treatment of bulbous urethral squamous cell carcinoma showed that wide local excision appears to give the best chance of survival without the morbidity associated with local recurrence. *En bloc* excision of the bladder, prostate, urethra, scrotum and perineal skin, together with excision of the anterior pubic arch, appears to lead to the best survival rates in a limited series of cases.

This rare urological tumour invades locally and is slow to metastasise. Penile urethral lesions are best treated with penile amputation and where indicated, pelvic or inguinal node dissection The difficult bulbous lesions would at present appear to be best treated by proximal diversion followed by wide local excision. The prognosis for lesions of the penile urethra is much better than that for bulbous urethral tumours

Complications of Groin Dissection in Penile Cancer: Experience with 101 Lymphadenectomies

By R. K. Lo and D. E. Johnson
M. D. Anderson Hospital, Houston, Texas, and Hong Kong

Groin dissections have been an integral part of the surgical management of regional lymphatic drainage for the staging and treatment of squamous cell carcinoma of the penis. Even though cures in approximately 40 to 50% of patients with lymph node metastases have been reported using an extended ilioinguinal node dissection, the procedure is not without its shortcomings. To assess the operative morbidity, we reviewed retrospectively 101 groin dissections performed in 67 patients from 1948 to 1983. There were no mortalities, but only 18% experienced no post-operative complications. Early complications included flap necrosis in 50%, seroma in 16%, wound infection in 14%, lymphocele in 9% and thrombophlebitis in 6%. Leg oedema developed in 50% of the operated extremities and remained severe in about one-third of these. There was no relationship between the rate of complications and the type, timing or extent of node dissection The frequency of complications has changed little over the 35-year time span of the study. Despite various reports of techniques to reduce the operative morbidity, caution should be exercised in the judicious selection of operative candidates.

In a separate analysis, the survival of 22 patients with histologically proven lymph node metastases was reviewed One of 8 patients who underwent a delayed, therapeutic node dissection survived for 5 years, whereas 8 of 14 patients who had a prophylactic dissection were alive at 5 years Sentinel node biopsies should be performed to select patients for therapeutic lymphadenectomies.

Keith Kirkland Prize Presentations

* indicates prizewinning essays

*Effects of Verapamil in the Prevention of Warm Ischaemia Induced Acute Renal Failure

By D. R. Eisinger, M. G. Suranyi, A. Farnsworth, P. Bracs and A. G. R. Sheil
Royal Prince Alfred Hospital, Sydney, New South Wales

Acute renal failure in the immediate post-operative period remains a significant complication of renal transplantation. A major fact in the pathogenesis may be warm ischaemia (WI) Recent evidence implicates a calcium mediated mechanism as a final common pathway in certain models of acute renal failure. This study was undertaken to evaluate the effects of verapamil, a calcium antagonist, in the prevention of warm ischaemia induced acute renal failure following renal autotransplantation in the dog. Twenty-one mongrel dogs were randomly allocated to three groups. Group 1 (control) (8 dogs) received 20 ml normal saline before a standardised 60-min warm ischaemic insult to the left kidney Group 2 (6 dogs) received verapamil (0.3 mg/kg) by intravenous injection and group 3 (7 dogs) received verapamil (0.3 mg/kg) by intra-arterial injection into the left renal artery prior to the same ischaemic insult. The left kidney was heterotopically grafted to the right iliac fossa in the warm ischaemic period. Contralateral nephrectomy was performed.

The dogs were followed up to 7 days after operation by serial creatinine estimation.

Of the 8 controls, 6 showed marked renal impairment (serum creatinine greater than 800 or death in renal failure). Three of the 6 dogs given intravenous verapamil showed marked renal impairment. None of the 7 dogs receiving intra-arterial verapamil showed marked renal impairment ($P<0.013$ χ^2 test). The mean rate of serum creatinine rise for each group was examined by multivariate analyses of variance. There was a significant reduction in the rate of creatinine rise in the intra-arterial group ($P<0.03$) There was significant correlation (Spearman rank correlation $P<0.01$) between the creatinine levels and the severity of histological damage. It was concluded that intra-arterial administration of verapamil prior to warm ischaemic insult reduced the incidence of marked renal failure and rate of post-ischaemia serum creatinine rise.

Evaluation of an Immunoperoxidase Technique for the Detection of Blood Group Antigens in Bladder Cancer

By M. R. Fraundorfer
Dunedin, New Zealand

Loss of cell surface blood group antigens in superficial bladder cancer has been associated with a high incidence of subsequent invasion. Conversely, tumours retaining these antigens are unlikely to invade.

The majority of workers have until now used the specific red cell adherence (SRCA) test to detect blood group-antigens Immunoperoxidase methods, however, are technically simpler to perform and in theory much more sensitive, particularly in blood group O patients.

In this study a commercially available immunoperoxidase method was employed using monoclonal mouse antibodies to human blood group antigens, A, B and H supplied by the DAKO Corporation.

The original biopsy specimens of 67 cases of superficial bladder cancer with a complete 5-year follow-up were evaluated. Of the antigen positive tumours, only 2 of 42 cases (5%) subsequently invaded, whereas 16 of the 25 antigen negative cases (64%) invaded This difference is highly significant and closely approximates the combined results reported in the world literature using the SRCA test. Antigen positive tumours also had significantly fewer recurrences per year than antigen negative tumours (0.8/year compared with 1.42/year). The percentage of antigen positive tumours in blood group O patients was similar to that of the series overall

This study, using immunoperoxidase techniques, has again confirmed the prognostic value of blood group antigenicity in bladder cancer. Antigenicity studies would be most useful in those patients with superficial disease for whom radical therapy is being contemplated. Preservation of antigens in such cases should encourage continued conservative management.

Correlation of Cytology and Endoscopy in Bladder Cancer

By R. I. Hill
Department of Surgery, Flinders Medical Centre,
Bedford Park, South Australia

The role of urinary cytology in bladder cancer falls into three main categories: firstly, the diagnosis of carcinoma *in situ*; secondly, the detection of an occult urothelial malignancy in the kidney or ureter, prostatic ducts or diverticula; thirdly, the surveillance of those with a greater risk of developing malignancy

In a survey of records of 108 patients with a history of bladder cancer, 429 observations were made correlating the results of cytology with those of endoscopy. Cytological examination of voided samples collected within 1 week prior to endoscopy were reported by a single observer.

Of the 429 cytology reports, malignant cells were identified in 43 (10%), atypical cells in 109 (25%), no suspicious cells were seen in 233 (55%) and the specimen was unsatisfactory in 44 (10%). In 35 of the 43 positive specimens, overt tumour was found, leaving 8 false positives Of these 8, random biopsy showed severe dysplasia in 5 and carcinoma *in situ* in 2. In 109 reports of atypia, 46 had tumours and a recognised cause for the atypia (*e.g* dysplasia, past chemotherapy, infection) was present in 40 others. Fifty tumours were found in the group of 233 with negative cytology; 44 of the tumours were Grade I. Most unsatisfactory specimens contained too few cells for evaluation but 20 of the 44 were found to have tumour.

Sensitivity of urine cytology in this series was 62% (*i.e.* 38% false negatives). Specificity was 97% with only 8 false positive reports where overt tumour was not found at endoscopy These figures are in accord with most series in the world literature

Catheter Induced Urethritis: Clinical and Experimental Studies

By J. N. Nacey, B. Delahunt, A. G. S. Tulloch and A. F. Ferguson
Departments of Urology and Pathology Wellington Hospital, Wellington, New Zealand

A controlled randomised prospective study was carried out on 100 male patients to compare the incidence of urethritis following catheterisation with either a brand of latex or a brand of silicone Foley catheters. All patients underwent elective cardiac surgery and were catheterised for 48 h with antibiotic cover. All patients were followed for a 6-month period The results show a statistically significant difference in the incidence of urethritis using the latex catheter as compared with the silicone catheter group (11/50 *vs* 1/50, $P<0.01$). Only 2 of the 100 patients showed a diminution in urinary flow rate and both of these had been troubled by urethritis following insertion of latex catheters. Both of these had tight anterior urethral strictures. Ascending urethrograms on all other patients who had been troubled by urethritis showed no abnormality.

In view of the clinical findings a new experimental dog model was established to compare the incidence and severity of urethritis using other Foley catheters of varying composition. In this model a scrotal urethrostomy was performed and catheters left indwelling in the anterior urethra. The catheters were left in the urethra for 48 h. The dogs were then sacrificed, and the urethra sectioned and examined for inflammatory change on the basis of degree of ulceration and active inflammation. From the clinical trial it was expected that the silicone catheters would produce less inflammatory change than the latex catheters and indeed this was the case. Three silicone and three silicone coated catheters of different brands were tested and all six catheters produced only mild inflammatory change with an intact transitional epithelium. Twelve latex catheters of different brands were tested and all of these produced moderate to severe changes, some with partial, almost full thickness ulceration of the transitional epithelium.

*Destructive Testing of Sutures in Infected Urine

By L. C. Thompson, W. H. Round and
C. A. Appleton
Royal Brisbane Hospital, Brisbane, Queensland

Polyglycolic acid, polygalactin, and chromic catgut sutures of 4/0 gauge were incubated for up to 10 days in sterile saline, sterile urine from a volunteer, urine from a volunteer inoculated with *Escherichia coli* and urine from patients with an *Escherichia coli* infection.

The tensile strength of the sutures was measured daily

After 10 days the tensile strength of the sutures incubated in sterile saline and in sterile urine from a volunteer was not significantly decreased.

The artificially inoculated sterile urine dissolved the polyglycolic acid and polygalactin sutures on the tenth day but the chromic catgut sutures maintained their strength.

The polygalactin and polyglycolic acid sutures incubated in urine from patients with a proven *Escherichia coli* infection dissolved on the third and fourth days respectively. Again the chromic catgut retained its strength to the tenth day.

The results from this *in vitro* study suggest that chromic catgut sutures are preferable to polyglycolic acid and polygalactin sutures in reconstructive urological surgery when infection is a possible complication.

Incontinence

Urodynamic View of Female Incontinence Procedures

By R. Turner-Warwick
Middlesex Hospital, London, UK

In addition to restoring the urethra into a surrounding intra-abdominal pressure environment, the functional effect of urethra-elevating incontinence procedures can be usefully classified into three groups according to the degree of passive urethral obstruction they create. The Periera-Stamey and U-sling procedures depend largely or entirely upon the creation of a passive partial obstruction of the urethra/bladder neck; they are more often effective in preventing leakage but tend to augment or create voiding inefficiencies.

Simple repositioning procedures such as anterior colphorrhaphy and the TW retropubic vagino-obturator-shelf (VOS) procedure elevate the urethra without creating primary urethral obstruction or secondary sphincter tethering. Continence after these procedures depends upon an improvement of intrinsic sphincter function because even the most effective repositioning of an inert urethra into the abdominal pressure zone does not render it competent unless there is an additional element of passive obstruction. Non-obstructive repositioning procedures rarely result in post-operative voiding difficulties and sometimes even improve a pre-existent voiding inefficiency associated with under-active detrusor and vesicourethral prolapse distortion.

Between these obstructive and non-obstructive procedures, the Marshall Marchetti urethral fixation and the Burch "colposuspension" procedures introduce a somewhat unpredictable element of para-urethral sphincter-tethering and suspension compression which may improve the leakproof results but also introduces an incidence of voiding inefficiency.

This study analysed the potential of the "functionally pure" VOS procedure in three groups of 25 stress incontinence patients. Twenty-five had stable stress incontinence without previous operation; of these 21 claimed dryness (5 showed minimal leakage) and 3 were much improved.

Of 25 patients who had stable stress incontinence after previous incontinence surgery, 15 (65%) claimed dryness (4 leaked minimally) and 3 were much improved.

Twenty-five patients demonstrated an associated low-pressure detrusor instability (P iso 50 cm/H_2O). Of these 14 (60%) claimed dryness, while 6 leaked occasionally and 4 were "much improved"

Thus for younger patients attempts were made to restore natural sphincter function by simple repositioning. Instability associated with stress incontinence is not a contraindication provided that it is a low pressure detrusor instability

Detrusor Instability and Incontinence. Which Patients Can be Cured?

By J. B. Wheelahan
Queen Victoria Medical Centre, Melbourne, Victoria

There is disagreement over whether patients with detrusor instability can be cured by colposuspension.

One hundred women (12 normal control, 88 incontinent non-neuropathic patients) were studied by a filling cystometrogram and voiding study and the data transformed using a microprocessor to provide a plot of detrusor pressure against volume, giving a graphical representation of bladder filling and micturition.

Those patients with a detrusor contraction sustained down to a small bladder volume have a good result from colposuspension if they have sphincter weakness (resting maximum urethral closure pressure <65 cm H_2O), regardless of the presence of detrusor instability. A low detrusor voiding pressure also reflects sphincter weakness. If sphincter weakness is absent, response to drugs is good.

For patients with detrusor instability and a poorly sustained voiding detrusor contraction, the results of treatment are poor. This group appears to have a type of detrusor failure and has lost normal voluntary detrusor function.

Study of the active phase of micturition is a key to understanding detrusor instability, and women with a sustained, voluntary detrusor contraction have a benign disorder of bladder function which is not a contraindication to colposuspension.

Colposuspension and the Management of Stress Incontinence

By C. U McRae, E. P. Arnold and S. P. Gowland
Christchurch Hospital, Christchurch, New Zealand

Assessment of the clinical result of colposuspension was undertaken by a questionnaire sent to 97 women who had undergone colposuspension for stress incontinence with a mean follow-up time of 19 months. Assessment was made of clinical presentation and the clinical result of operation Urodynamic studies, although done in many patients, were not considered in this report. Eighty-six completed replies were available for evaluation and of these 75 patients stated they were completely or almost completely dry. Age and pre-operative symptoms of urgency or urge incontinence had little effect on the likelihood of a successful outcome but those who had had previous anti-incontinence surgery had a lower chance of a successful result. Symptoms of urgency and urge incontinence improved in 29 of 57 patients with these symptoms. Urinary frequency improved in 23 of 54 patients with pre-operative significant frequency. Minor obstructive symptoms were noted on a persistent basis by 30 patients and 13 felt the operation had significantly worsened their sexual activity. Overall, 92% claimed the operation had been totally or partially successful.

Colposuspension is considered to be a reliable and effective operation in stopping clinical stress incontinence but clinical results such as these need to be assessed along with urodynamic results.

Treatment of Vesicovaginal Fistula Using the Martius Procedure

By S. Sihombing
Division of Urology, Department of Surgery,
University of Padjadjaran, Bandung, Indonesia

As Indonesia belongs to one of the developing countries, the incidence of vesicovaginal fistula caused by obstructed labour is still high. Nineteen cases considered to be difficult and/or after several unsuccessful attempts at closure, were referred to our department between 1980 and 1983. Patients were from 16 to 60 years of age. All of the fistulae were located low down in the anterior wall of the vagina, none involved the ureteric orifices and some involved the bladder neck and urethra. This seems to be the characteristic of vesicovaginal fistula caused by obstructed labour. Two of the fistulae were 1.5 cm in diameter and 17 ranged from 3 to 4 cm. Of the large sizes, 5 involved the bladder neck and/or urethra; in 2 of these, the urethra seemed to be transected and adhered to the pubic bone, 3 were complicated with rectovaginal fistula and 2 others with bladder stones. The time lapse between the occurrence of the fistulae and the referral was from 5 months to 35 years.

The Martius procedure was used to treat all cases. By adding 4 incisions perpendicular to the usual circular dissection incision—2 transversally and 2 vertically (directed to the urethra and the cervix)—sufficient dissection can be obtained to release all adherent tissue and make possible the approximation of freshened edges of the fistula without tension. Watertight suturing of the bladder fistula was essential. Dependent drainage was used post-operatively for 2 weeks. Eighteen of the 19 cases (95%) closed successfully. In 3 cases temporary stress incontinence was present which disappeared within 3 months The Martius procedure is recommended for vesicovaginal fistula caused by obstructed labour before trying other more complicated procedures.

The Incidence of Urinary Incontinence in Australia. A demographic survey conducted in the Sydney area in 1983

By R. J. Millard
Prince Henry Hospital, Sydney, New South Wales

In September 1983 a survey was conducted to determine the prevalence of urinary incontinence in the general population over 10 years of age. A multi-stage cluster sampling technique was employed in 100 postal districts in the environs of Sydney. Self-administered questionnaires were distributed to 3000 persons in 1000 homes; 1256 replies (42%) were received and analysed

Six hundred and five males and 651 females over the age of 10 years replied. Comparison of the age distribution of the sample with census data shows close correlation overall with a slightly lower participation in the study by people aged 60 and over.

From this study it appears that urinary incontinence is extremely common in the population and that its incidence rises with age: 24% of individuals over the age of 10 years admit to some urinary loss and 6% of the population have significant or frequent urinary leakage.

Of those who currently have no incontinence (76%), 23% have experienced some urinary leakage in their past adult life. The male to female ratio amongst those who currently suffer some leakage is 1 to 2.7, that is 73% of sufferers are female. When incontinence is severe the male to female ratio rises to 1 to 7.5 (88% of sufferers are female). The female predominance disappears over the age of 60

In summary, the incidence of incontinence is as follows:

	Males	*Females*	*Overall*
Past incontinence (childhood)	25%	26%	26%
Past incontinence (adult life)	16%	30%	23%
All present incontinence	13%	34%	24%
Never incontinent as an adult	28%	53%	41%
Significant incontinence now	2%	11%	6%

By applying the figures for significant present incontinence to the census figures for the state of New South Wales it is estimated that as many as 251,000 persons in this state may suffere from incontinence. This equates to a total of 738,000 sufferers throughout Australia Less than half of these ever seek professional help.

Calculus Disease

Early Experience with Percutaneous Stone Surgery

By I. Nunn
Royal Melbourne Hospital, Melbourne, Victoria

The results of the first 39 consecutive patients who underwent percutaneous renal stone surgery were presented.

Nineteen had calculi extracted and in 13 the stone was disintegrated using an ultrasound probe. In these 39 patients there were 10 failures—more than 25%. However, 3 were successfully treated at a second attempt. In 3 patients the stone had moved prior to operation. This was not evident on the pre-operation plain film and a careful pre-operative nephrostogram is recommended rather than the former as the relationship of the opacity and renal pelvis may not be apparent. Two other patients dislodged the nephrostomy tube on the way to theatre. A ureteric guide wire is now used as well as a nephrostomy tube so that the situation can be retrieved

One patient who had a stone which would not disintegrate and another in whom the stone could not be seen because of constant "red out" constitute the two real failures of the technique.

It is apparent that the major cause of failures is inexperience in the technique and attempting it in inappropriate circumstances

One serious complication of periureteric fibrosis and pelviureteric junction obstruction has occurred.

Ten patients had residual fragments; most have been cleared by extraction, washout, or spontaneous passage. In two there were fragments deliberately left in the middle calix but another two still have tiny residual opacities which have not been eliminated. The remaining post-operative problems were minor and temporary.

Hospital stay was short. The post-operation interval was between 2 to 5 days and normal activity was commenced within a week in the majority.

Experience suggests this surgical technique can achieve outstanding results if a careful selection of patients is made and an experienced radiologist-surgeon team is available.

Hazards of Stone Destruction by Ultrasound

By J. G. Brockis, W. K. Jones and R. A. Fox
Royal Perth Hospital, West Australian Government Public Health Department, Perth, Western Australia

This study attempted to evaluate the risk to the operators from ultrasonic kidney stone destruction probes. The use of such probes in percutaneous surgery for urolithiasis is now common practice all over the world. Sufficient attention may not have been paid to the risks that the operators of these machines may face. Ultrasonic probes use sound pressure waves at frequencies above 20 kHz (normal hearing extends up to about 15 kHz in the average adult), so these sound waves are not audible to the human ear. The human ear is peculiar in that it hears sound levels in a logarithmic way and for that reason the measurement of sound pressure waves is evaluated on a logarithmic scale of decibels. Very high sound levels can be damaging to the human ear both to the cochlea and vestibular apparatus. The typical effects are of hearing loss, tinnitus and dizziness. For that reason governments throughout the world are now laying down standards and at the Tenth International Congress on Accoustics in Sydney, 1980, maximum safety levels were suggested. Governments in different areas vary slightly in the levels they permit. As yet Australia has not proclaimed any regulations relating to sound levels in industry, though state governments are looking at this problem. The machines commercially available to urologists have a fundamental frequency between 22 and 28 kHz but also emit a whole range of other frequencies.

Recordings have been made 4 cm from the ultrasound generator, that is the distance which the human ear is from the probe in the operating theatre. At 25 kHz there are 110 dB of sound, which is the maximum level laid down by the congress. Evidence exists that other probes give recording levels of 127 dB at 25 kHz and, worse still, faulty probes may give 110 dB at 11 kHz, which is 30 dB above the safety level of 80 dB. Ultrasonic probes are notoriously temperamental and a crack in the ceramic generator or a loosening in its housing can alter the frequencies emitted quite dramatically. Such an alteration may not necessarily be accompanied by loss of efficiency of the probe, the main problem being the danger to the operator Risks to the operator are too great with the present generation of probes unless some protection is afforded. In the future the manufacturers may be able to reduce the level of extraneous sound reaching the ear with some sort of baffle, but until they are able to do this it is believed that the wearing of earmuffs by the operator is necessary. The Wilson Model 358A earmuff will reduce sound levels by 20 dB Furthermore, probes should be tested regularly because their characteristics may change.

There appears to be little danger to anyone other than the surgeon in the operating theatre as the levels fall to acceptable values 20 cm from the probe, which means an assistant is not at risk.

Partial Nephrectomy in Renal Calculus Disease

By R. W. Fletcher, P. T. Bruce and
J. B. Wheelahan
Queen Victoria Medical Centre and Sandringham and District Memorial Hospital, Victoria

A retrospective analysis of experience with partial nephrectomy performed for calculus disease in 32 cases was presented with a mean follow-up of 4 years. The indications for surgery included loin pain, haematuria and infection.

Partial nephrectomy was indicated for the following reasons. Technical consideration included the size of calculus, multiplicity of stones or poor calcification (14 cases). Localised parenchymal disease was indicated by caliceal clubbing or intrarenal calcification (16 cases), while recurring or persisting infection was present in 13 cases. Nine patients were recurrent stone formers

Guillotine amputation was performed in most cases, the renal artery being temporarily occluded with an encircling soft red rubber tube secured with curved artery forceps.

Incomplete stone removal occurred in 3 patients; two had an associated *Proteus* infection and required delayed nephrectomy for sepsis or calculus regrowth. One patient developed a new calculus. This represented a recurrence rate of less than 4% in 4 years' follow up. One patient had significant secondary haemorrhage requiring transfusion. At follow-up IVU, normal renal function was demonstrable in all cases with no evidence of delayed vascular damage or renal atrophy

Partial nephrectomy still has a place in the management of patients with calculi, particularly in those with multiple localised renal calculi to upper or lower calices and in cases of recurrent calculi formation. The low morbidity and low recurrence rate are the standards by which other procedures, particularly percutaneous nephrostomy extraction, may be judged. Poor results are to be expected if incomplete stone removal is achieved in the presence of renal infection.

Impotence

Difficulties Experienced in the Assessment of Erectile Impotence

By R. A. Cartmill
Royal Brisbane Hospital, Brisbane, Queensland

The development of penile prostheses has led to increased interest in the assessment and management of erectile impotence and during the last decade, many reports have appeared in the urological literature. This study related experiences and difficulties in the assessment of impotence in a clinical practice within Australia The assessment following the history and clinical examination used the services of a psychiatrist and an endocrinologist, as well as nocturnal penile tumescence studies and penile blood pressure measurement. It is important that both patient and partner be involved in this assessment programme so as to maximise the clinician's understanding of the importance of the sexual dysfunction to the couple.

Two hundred and eight patients were considered for treatment after declaring some form of sexual dysfunction· 181 chose to have a detailed consultation which allowed an explanation of the assessment programme as well as the available treatment. Of these, 52 patients declined to proceed with the assessment, while a further 38 were judged unsuitable for assessment. Hence, only 50% of the originally presenting patients underwent the assessment programme Following assessment, a further 28 patients were judged unsuitable for surgery or declined surgery of their own volition. The end result was that only 30% of the original group of patients were suitable for surgical management of their impotence It was found that an interest in treating organic erectile impotence led to a number of patients presenting with a variety of sexual and functional disorders. The assessment of these patients was time-consuming and involved the urologist in the role of marriage guidance counsellor offering advice normally given by psychiatrists, and having to give advice on social and theological questions.

The review of the patients further suggests that the psychiatric opinion does not alter the original impression of the patient, but merely confirms the original impressions. Nocturnal penile tumescence studies, although often criticised in the literature, were found to be beneficial, although this was largely due to the availability of a technician who could verify the normality or otherwise of the erection and hence increase the accuracy of the nocturnal recordings.

Only 30% of patients were found to be suitable for surgery in this series. While this will vary with the referring pattern, it is apparent that the majority of patients presenting with some form of sexual dysfunction do not require surgery.

The Assessment of Patients and their Wives After Insertion of the Jonas and AMS Inflatable Prostheses

By A. G. S. Tulloch, B. Adler, Catherine H. Cole, A. Kermode, Janine L. Spencer, A. Vickery, E. R. Csillag and E. J. Keogh
Sir Charles Gairdner Hospital, Perth, Western Australia

Since 1974, the first author has carried out 30 implantations with the AMS inflatable prosthesis and 66 implantations with the Jonas prosthesis Seventeen revisions of the AMS inflatable prosthesis have been required, two for reservoir leaks and 14 for cylinder leaks, and one for pump erosion. One patient was converted to a Jonas prosthesis. With the Jonas prosthesis, four revisions have been required—two for fractured wires and two for replacement with a longer prostheses because of a deformity with a flaccid glans penis. In three patients who were severe diabetics, infection developed which required the removal of the prosthesis.

Forty-seven patients who had had the prosthesis in place for more than 6 months were interviewed in their homes by a medical student (BA, AK or AV). There was no statistical difference between the measurement of overall satisfaction and sexual satisfaction depending on the type of prosthesis used. However, 60% of the patients with the Jonas prosthesis have difficulty in concealing the prosthesis beneath clothing compared with only 25% of those patients with the AMS inflatable prosthesis. The study demonstrated that impotence was associated with marital conflict and penile prosthesis implantation was associated with a significant improvement in marital harmony. To the investigators' surprise, the most satisfied group were those patients over the age of 60.

Twenty-eight wives of patients who had been successfully implanted were interviewed. Two female medical students (CHC and JLS) visited the wives in their homes to discuss the results of surgery. Of the wives, 18 were satisfied, 6 were neutral and 4 were dissatisfied with the surgical results. Fourteen wives recorded difficulty with penetration and 12 noted that the penis bent and made intercourse difficult. Ten wives were concerned about the artificiality of the penis The investigators felt that the best results were obtained if wives were involved in the decision whether or not to proceed with surgery, and that sexual counselling should be available and may indeed be crucial to the success of a penile prosthesis implantation.

Experimental

Increased Levels of Dihydrotestosterone Receptors in High Stage Renal Carcinoma

By R. F. C. Noronha, C. M. G. Goodall and B. D. Rao
Dunedin, New Zealand

Primary renal carcinoma, metastatic deposits and normal kidney parenchyma from 16 patients were assayed for sex hormone receptors by dextran-coated charcoal and sucrose adsorption techniques.

Dihydrotestosterone receptors (DHTR) were found in all renal carcinomas (20/20) and in 93% (13/14) autologous normal kidneys analysed. Testosterone receptors were found in 84% of tumours and 93% of normal kidneys, oestrogen receptors (ER) in small amounts were detected in only 5% of tumours and 7% of normal kidneys; progesterone receptors in low quantities were detected in 30% of renal tumours and in 40% of normal kidneys

DHTR levels in high stage tumours (T3, T4) were significantly elevated over levels in autologous normal kidney In low stage tumours localised to the kidney (T1 and T2 tumours) DHTR levels were not significantly different from levels in autologous normal kidney.

The mean levels of DHTR in high stage kidney tumours were significantly elevated over levels in low stage tumours ($P<0.001$).

Intrarenal Access: The Long-term and Short-term Effects on Renal Function and Structure

By J. D. Taylor, K. B. Shilkin, T. York, A. Storrie and D. E. Hartley
Sir Charles Gairdner Hospital, Perth, Western Australia

The effects of extensive renal incisions in 20 dogs were examined at 2, 7 and 42 days by three techniques serial biochemistry, histological examination, and gelatin barium arterial injection with magnification radiology. The results indicate that single longitudinal and double transverse full thickness incisions of the renal parenchyma produce early distortion and functional loss but only minor permanent damage. Double longitudinal bivalve incisions cause extensive permanent loss of function and much necrosis. No divided renal vessel was ligated. The pelvicaliceal system and capsule were closed with continuous sutures. Healing of cortex, medulla and particularly papillae was by linear scar without infarction for single bivalve and double transverse full thickness incisions.

It is postulated that the early reversible loss of renal function and parenchymal distortion are due to haematoma formation within the relatively inelastic kidney capsule.

It is accepted that there are usually no adequate anastomotic channels between the major segmental renal arteries. The absence of necrosis in this study indicates a potential collateral arteriolar supply within each segment It is therefore suggested that it is pointless to seek out a bloodless plain between anterior and posterior segmental renal arteries when undertaking an anatrophic nephrolithotomy. There is also no need to ligate divided vessels. Authors who have done so report renal infarction.

Observations on the Factors Influencing Urethral Relaxation During the Initiation of Reflex Voiding in Non-human Primates*

By J. R. Hindmarsh
Institute of Urology, London, UK and
Margaret Rose, R. J. Millard and G. F. Murnaghan
University of New South Wales, Sydney

An animal model has been developed to study the sequence of events that occur in the lower urinary tract on initiation of reflex micturition and the alterations that can be made by pharmacological manipulations.

Continuous monitoring of peak urethral pressure and bladder pressure during bladder filling and voiding was performed in 12 female *Macaca nemestrina* (pig-tailed monkeys) using two microtip tranducers mounted on a 5F catheter. Recordings were made of the normal urethral response to filling and voiding as well as after pharmacological manipulation of the automatic nervous system by alpha, beta, muscarinic and ganglionic blockades.

In the intact animal the onset of micturition was heralded by a substantial fall in urethral closure pressure which preceded the earliest rise in detrusor pressure. The urethral closure then decreased to its lowest level but the detrusor pressure started to rise slowly. When the detrusor pressure equalled the urethral pressure, then leakage of fluid occurred around the filling catheter and before the rise of detrusor pressure reached its peak. The subsequent decline in detrusor pressure was followed by a rise in urethral closure pressure to the pre-filling level.

Initiation of the reflex voiding sequence was delayed by atropine and beta blockade (propranolol). The voiding sequence was abolished by ganglionic blockade (pentolinium). The urethral closure pressure during bladder filling was dramatically reduced by alpha blockade (phentolamine) but this blockade did not influence the volume at which the reflex void was initiated.

The time course of urethral relaxation and the fall in urethral closure pressure were not altered by beta blockade or by atropine.

In non-human primates the initiation of a voiding sequence may depend upon beta receptor activation via a neural pathway involving autonomic ganglia

Radiological Studies of the Canine Urethra and the Effects of Prostatic Hyperplasia

By W. Poogird and A. K. W. Wood
Department of Veterinary Clinical Studies, University of Sydney, New South Wales

In dogs, little attention has been given to the radiological appearance of the urethra in retrograde and voiding urethrography and whether this appearance is altered in prostatic hyperplasia. Radiological studies were undertaken in nine mature male dogs, divided into three groups. In each group, prostatic hyperplasia was induced in two dogs by intramuscular injection of 25 mg 5-alpha-dihydrotestosterone, suspended in either sesame seed oil or in Triolein, 3 times weekly for 4 months. The third control animal was injected with the suspending agent alone

Before the commencement of each experiment, and at the end of each month, radiological observations were made with an 800 mA X-ray generator (Toshiba), caesium iodide image intensifier with television chain, videotimer and videocassette recorder (yielding 50 field/s) and 105 mm camera (4 frames/s). The dogs were anaesthetised (halothane and oxygen) and retrograde urethrography was performed. Then the bladder was distended with 280 to 360 ml contrast medium (15% sodium and meglumine diatrizoate) until a vesical pressure of 40 to 60 mmHg was reached and further observations were made as the dog voided during recovery from the anaesthetic. Each dog was necropsied at the completion of the experiments.

In both treated and control animals, retrograde urethrography showed that the diameter of the prostatic urethra was narrowed, in contrast to voiding urethrography when this region was dilated. At the middle and completion of voiding there were strong progressive contractions of the intrapelvic part of the urethra, which

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* These studies were supported by a grant in aid from the Australian Kidney Foundation

commenced just caudal to the prostate and progressed caudally to the level of the ischiatic tuberosities. In the control dogs urethral contractions occurred at a rate of 1.80 ± SE 0.06/s (n = 30). In the treated animals urethral contractions at the commencement of the experiment were at a rate of 1.60 ± 0 14/s (n = 30) and at the completion 1.80 ± 0.39/s (n = 30); these differences in the rate of urethral contraction were not statistically significant.

The results of this canine study indicate that in induced prostatic hyperplasia, urethral motility is of the same pattern and rate as in the normal urethra.

Experimental Studies on Testicular Development

By J. D. Taylor, K. B. Shilkin, T. York and Anne Storrie
Sir Charles Gairdner Hospital, Perth, Western Australia

When a solitary testis is present in the human, it is not always enlarged. This observation has led to an attempt to define the conditions under which enlargement of a solitary testis might be expected. In the first group of experiments, litters of Wistar rats underwent unilateral orchiectomy from the day of birth to day 15. In the second series of experiments unilateral cryptorchidism was induced in litters of Wistar rats serially from day 7 to day 15. All animals, including controls, were killed between day 90 and day 240, and the testes weighed.

The results indicate that from day 1 to day 12, unilateral orchiectomy induces compensatory enlargement of the remaining testis ($P < 0.005$). After day 12, the effect is not statistically significant ($P < 0.1$).

Unilateral cryptorchidism on the other hand does not produce compensatory enlargement of the contralateral testis when compared with the controls ($P < 0.1$) The cryptorchid testis rapidly atrophies ($P < 0.005$).

It is generally believed that there is active testicular function in the perinatal period This possibly results from a maternal gonadotrophin surge. Testosterone gradually decreases after birth. Sufficient testosterone is needed to imprint a negative feedback level on LH secretion

These experiments suggest that in the rats undergoing unilateral orchiectomy the setting of the level of negative feedback occurs at a critical time in the first 12 days. In unilateral orchiectomy there is lower testosterone and higher LH. The latter leads to testicular enlargement.

In the unilateral cryptorchid rats testosterone secretion is not impaired until after the critical period and thus the setting of the negative feedback level for LH is normal. Hence the descended testis is the same weight as in the controls.

Hormone assays have not been done in this series to confirm this hypothesis. They are currently being undertaken.

Endoscopic Transvesical Ureterotomy

By R. A. Gardiner
Royal Brisbane Hospital, Brisbane, Queensland

This technique was employed in two patients for whom established procedures for correcting lower uteric strictures were considered inappropriate.

The first woman had a post-irradiation stricture diagnosed 3 years after treatment for cervical cancer After TUR of a histologically proven benign nodule involving the right ureteric orifice, the ureter was dilated and then catheterised. Using a Colling's knife an incision was made completely through the posterior bladder wall, exposing extravesical fat, and through the ureteric wall at 12 o'clock, cutting into the catheter. The ureter was incised a distance of 1.5 cm from the new ureterovesical junction. The ureteric catheter was removed inadvertently on day 2 and the urethral catheter on day 7

Intravenous urography at 6 months demonstrated relief of obstruction. Videocystometrography showed 3/4 reflux only during voiding. The bladder was stable and unobstructed.

The second woman had a post-tuberculous stricture. She presented with right-sided pyelonephritis. Ureteric dilatation 4 months before endoscopic transvesical ureterotomy failed to relieve obstruction. The posterior bladder wall and extravesical ureter were incised as before but this time for a distance of 4 cm from the ureteric orifice, stone fragments being dislodged above the stricture at 3 cm This procedure was necessarily brief because of ventricular dysrhythmias during anaesthesia, so meticulous attention to bleeding points was not addressed Intermittent bladder irrigations were employed for 2 days with straight catheter drainage for 9 The ureteric catheter was dislodged in the recovery ward. Post-operatively there were symptoms and signs consistent with extravasation. The patient's urine has remained uninfected since the procedure.

Although intravenous urography at 3 months showed considerable improvement with caliceal cupping, some ureteric dilatation persisted. DTPA renography excluded obstruction, demonstrating an improvement in right-sided function from 30% pre-operatively to 40% of total renal function. Videocystometrography showed free reflux into the lowermost ureter only during voiding. The bladder was stable and unobstructed.

Miscellaneous

Diuretic Renography in the Diagnosis of Upper Tract Obstruction

By C. U. McRae and M. H. Moore
Christchurch Hospital, Christchurch, New Zealand

The distinction between obstructed and non-obstructed dilated upper tracts remains a difficult problem. There is at present no single test that consistently and reliably demonstrates obstruction in dilated systems. The diuretic renogram has gained wide acceptance but there has been no previous consideration of the likely diuretic effect of frusemide on a kidney with poor function.

Eleven patients were studied in whom the urine output from a normal kidney and an abnormal kidney could be collected separately. It was shown that in a group of abnormal kidneys with poor renal function there may be a little or no response to frusemide stimulation in spite of a normal response in the contralateral normal kidney. In children, although there may be a significant response to frusemide stimulation, the increase in volume may be insufficient to be significant in a very dilated system.

It is therefore suggested that consideration of the renal function of a kidney needs to be taken into account when interpreting diuretic renograms.

Superior Ectopic (Thoracic) Kidney

By F. D. Stephens
Children's Memorial Hospital, Chicago, USA

From an analysis of published case reports and the study of four *post morten* specimens, four types of superior ectopic kidneys were identified.

The kidneys were classified according to their relationship to the diaphragm into supra-, trans-, infradiaphragmatic and Bochdalek kidneys.

Supradiaphragmatic kidneys lay entirely retropleural above a normal diaphragm; transdiaphragmatic kidneys were commonest and part extrapleural and part extraperitoneal and the diaphragm fitted snugly around a circumscribed posterior defect with or without a thin fibrous membrane covering the part protruding infradiaphragmatic kidneys were high and retroperitoneal but beneath a thin eventrated diaphragm; the kidney associated with a Bochdalek hernia was rarely ectopic but occasionally it was mobile and rotated on its vascular pedicle into the defect or, more rarely, lay in an abnormally high position with an abnormally high origin of its renal vasculature.

The mechanism of migration to superior locations is intrinsic in the kidney and is an active migration rather than a passive rearrangement of structures in the growing organism. With supradiaphragmatic kidneys the migration precedes the formation of the posterior component of the diaphragm; with transdiaphragmatic kidneys the migration and development of the posterior component are synchronous and the remaining components mould around or "hourglass" the kidneys. With infradiaphragmatic superior kidneys the components of the diaphragm unite prior to the abnormal migration but remain eventrated and amuscular. With Bochdalek hernias the kidney rarely prolapses or migrates through a wider defect caused primarily by failure of formation of the pleuroperitoneal membrane. This defect results in confluence of peritoneal and retroperitoneal spaces with pleural and retropleural spaces respectively.

Superior ectopic kidneys other than the Bochdalek type are rare, symptomless, otherwise normal, fixed in the ectopic position, and on chest X-ray may mimic a neoplasm.

Jaboulay and the History of Hydrocele

By P. S. Lawson
St Vincent's Hospital, Melbourne, Victoria

Most students know hydroceles are cured by Jaboulay's operation. Who was Jaboulay and what did he describe? Mathieu Jaboulay was born near Lyon, France, in 1860 and later became Professor of Surgery at the Hospital of God in Lyon.

Besides his operation for hydrocele he described a number of other urological procedures. He was the first surgeon to transplant a kidney into a human.

The treatment of hydrocele was traced starting with formal incision in ancient India, the use of the Seton, the preference for cautery in Arabian centres, the use of injection therapy and then Jaboulay's original description of eversion of the hydrocele sac.

A biographical sketch of Jaboulay himself concluding with his untimely death in a train crash on the outskirts of Paris in 1913 was outlined.

Pre-urethral sub-puboprostatic Space and its Surgical Significance

By R. Turner-Warwick
Middlesex Hospital, London, UK

In front of the prostato-membranous urethra, in the position supposedly occupied by the anterior part of the mythological "urogenital diaphragm", there is a space which seems to be undescribed in spite of the fact it has considerable surgical significance.

Bounded anteriorly by the pubic symphysis, it lies below the pubo-urethral ligaments in the gap between the inner margins of the pelvic floor levators with the inferior pubic rami below them. Its roof is formed by the puboprostatic ligaments, its floor by the bulbar urethra and its encircling bulbospongeosus muscle, while posteriorly it is occluded by the fusion of the pubo-urethral element of the levators and the perineal body behind the membranous urethra.

The existence of the pre-urethral space became obvious during the development of reconstructive bulbomembranous procedures.

An appreciation of the intramural location of the distal sphincter mechanism is fundamental to the management of sphincter strictures and the dangers of internal urethrotomy in this area; the erroneous supposition of a funtional external sphincter muscle mass surrounding the membranous urethra has been responsible for its rough handling during both enucleation and radical prostatectomy in the past. The positioning of electromyographic electrodes anteriorly provides pure records of distal sphincter activity unadulterated by para-urethral pelvic floor muscle potentials.

Subprostatic pelvic fracture urethral injuries are almost invariably located at some level in the 1 to 2 cm related to the puboprostatic space; in minimal injuries the secondary haematoma is commonly localised by it.

The sub-puboprostatic space is used to locate Teflon injections for post-prostatectomy incontinence. Furthermore, using a synchronous perineoretropubic approach, it can be definitively developed by the division of the puboprostatic ligaments for the pre-urethral location of an inflatable incontinence prostatic balloon as an alternative to circumferential positioning around the bladder neck or bulbar urethra—using the perineal body and pubo-urethral sling structures as counter-pressure.

Experience with J-shaped Internal Ureteric Splints

By J. P. O'Collins

Prince Henry's Hospital, Melbourne, Victoria

Thirty-nine patients who had a double J ureteric splint inserted were reviewed. Their average age was 50 years (range 18-24). In 14 cases (35%) there were complications. The J-shaped splint could not be passed in 7 cases due to a lower ureteric obstruction. Carcinoma at the ureteric orifice prevented passage of the splint in 4 cases and in a further 3 there was "kinking" of the ureter.

In a further 3 patients there was obstruction of the splint by calcareous material after 6 months and in a further 2 cases, calculi developed on the kidney on the same side as the splint and were again noted after a period of 6 months. One splint was "lost" up the ureter and required surgical removal, while in two cases the splints were passed too far into the kidney, causing haematuria.

Renal Venous Hypertension

By D. L. Murphy

Geelong, Victoria

Three cases of left renal venous hypertension, as related to the nutcracker phenomenon, were described. The patients presented with a combination of haematuria, anaemia, left flank pain and one with clinical left varicocele. Two had repeatedly normal renal biopsies.

Special investigations including angiography, augmented venography, differential venous pressures for the right renal vein, left renal vein and inferior vena cava, supine, standing, with and without Valsalva, were conducted. Renal venous CT was performed as an appropriate pre- and post-operative, non-invasive test.

Surgical treatment was performed in two cases by left renal vein lowering, out of the nutcracker area, with adrenal vein division and without renal mobilisation or ligation of varicosities.

Clearance of the haematuria and relief of pain for both patients was achieved as well as decrease in the volume of the varicocele. The third patient is to be further assessed.

British Journal of Urology (1985), **57**, 106–115

Case Reports

Unusual Complication of Foreign Body in the Bladder

A. KACZMAREK, *Department of Urology, Railway Hospital, Wroclaw, Poland*

Case Report

A 43-year-old married man was admitted for removal of a foreign body in the bladder. Seven days previously a ballpoint pen had been inserted into the bladder through the urethra by an occasional sexual partner. Since that time the patient had had discomfort in the suprapubic region, painful and frequent micturition and terminal haematuria.

Physical examination was normal. Urine analysis revealed numerous white and red blood cells. Cystoscopy confirmed the presence of a ballpoint pen obliquely positioned in the bladder. One hour after cystoscopy, while attempting to urinate, the patient felt sudden acute pain in the hypogastrium. Examination revealed tenderness and rebound tenderness and obvious peritoneal involvement. Cystography showed a foreign body about 10 cm long in the bladder (Fig.). It was lodged longitudinally from the bladder neck to the dome with perforation of the bladder and discharge of contrast material into the peritoneum.

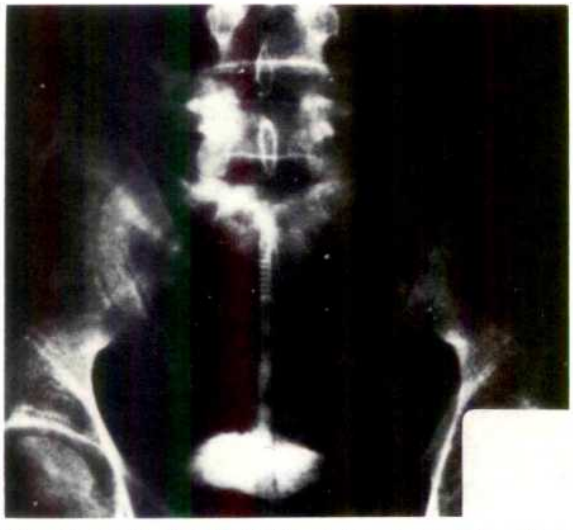

Fig. Urography showing discharge of contrast substance from the bladder into the peritoneal cavity.

At operation it was found that the sharp end of the pen had perforated the anterior wall of the bladder in the region of the dome. One half of the pen was lodged in the peritoneal cavity and the other half in the bladder lumen. The pen was removed and the bladder perforation sutured. The patient made an uneventful recovery.

Comment

The great variety of foreign bodies in the bladder is surprising but serious complications are rare (Kiriyama *et al*., 1976).

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Requests for reprints to: A. Kaczmarek, Department of Urology, Railway Hospital, ul. Wiśniowa 36a, 53-137 Wroclaw, Poland.

Malignant Fibrous Histiocytoma of the Bladder

A. J. GOODMAN AND M. G. GREANEY, *Derbyshire Royal Infirmary, Derby*

The first reported case in the United Kingdom of a malignant fibrous histiocytoma of the bladder is presented.

Case Report

A 61-year-old West Indian man presented with a history of increasingly severe suprapubic pain (worse on micturition), frequency, nocturia and persistent haematuria for 6 months associated with suprapubic tenderness and a smoothly enlarged prostate. Intravenous urography demonstrated a tumour of the right side of the bladder partially compressing the right ureteric orifice (Fig. 1). The presence of a solid tumour was confirmed at cystoscopy, when the tumour was noted to be mobile and extending to the right of the pelvis. Histological examination revealed a spindle cell tumour; arising in the muscle of the bladder and producing collagen, it appeared to be a malignant fibrous histiocytoma (Fig. 2).

Total cystectomy with formation of an ileal conduit was performed; there was no evidence of intraperitoneal spread at operation and histological confirmation of the diagnosis was obtained. After 5 months the patient developed a small intestinal obstruction and laparotomy showed widespread peritoneal metastases. A palliative ileocolic anastomosis was performed but the patient died

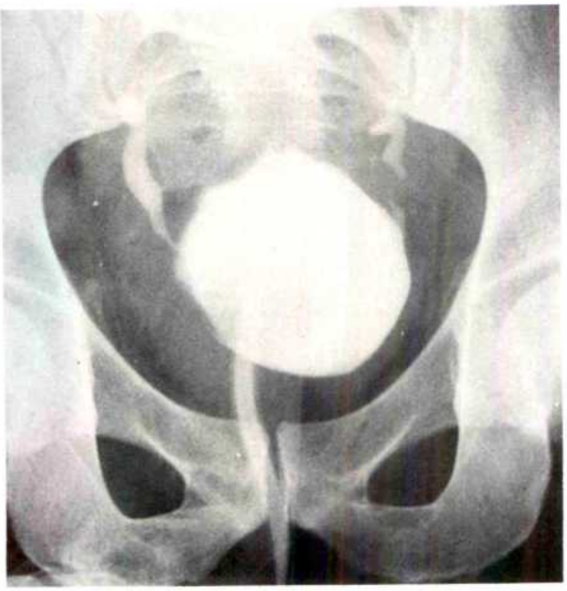

Fig. 1 Intravenous urogram demonstrating a filling defect in the right side of the bladder.

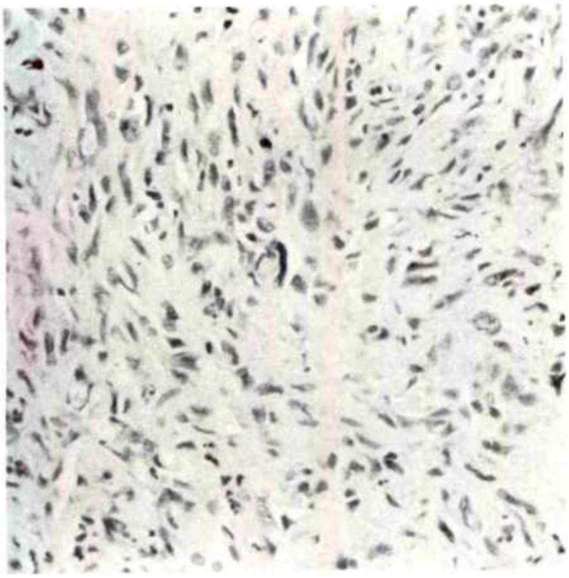

Fig. 2 Infiltrating spindle cell neoplasm with occasional multinucleate giant cells. The tumour cells are pleiomorphic and show foci of "storiform" arrangement. The appearance are those of a malignant fibrous histiocytoma (H and E × 168).

shortly afterwards. Biopsy of one of the deposits confirmed malignant fibrous histiocytoma.

Comment

Only three cases of tumours developing from histiocytes involving the bladder have previously been reported (Usher *et al.*, 1979). The tumours are usually benign (Karol *et al.*, 1977) and in only one of those patients was local resection followed by the appearance of metastases.

In the case presented, ablative surgery did not prevent an aggressive tumour reasserting itself and killing the patient.

Acknowledgement

We thank Mr K. W. Munson for permission to report his patient and for advice with the manuscript.

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Requests for reprints to: A. J. Goodman, 36 Highgate Drive, West Knighton, Leicester.

Giant Anterior Urethral Calculus Associated with Hypospadias and Congenital Meatal Stenosis

B. M. S. AL-SALEH, I. H. AL ALI, E. ANSARI and S. ADAM, *Department of Urology, Abu Dhabi Central Hospital, Abu Dhabi, United Arab Emirates*

Urethral calculi are rare and usually associated with urethral strictures or diverticula. The majority originate as renal or vesical stones. Primary ones occur rarely in men with true congenital meatal stenosis. We report a giant anterior urethral calculus in a patient with hypospadias and congenital meatal stenosis; the stone had been present for more than 25 years without causing urinary or sexual problems.

Case Report

A 29-year-old man was admitted with a 2-day history of dysuria, haematuria and fever. The patient described a "lump or bone structure" that had been present below the glans penis since childhood and had gradually increased in size. Until the onset of severe dysuria there had been no significant urinary symptoms except that

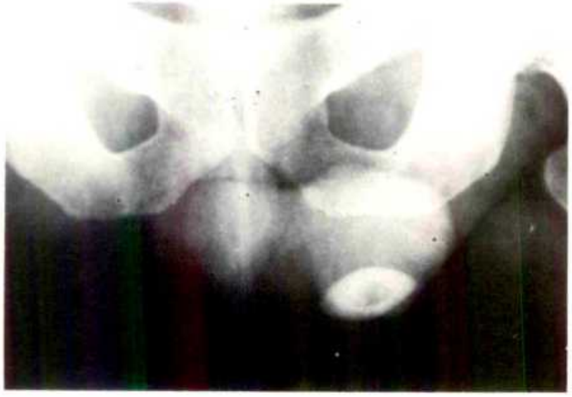

Fig.

occasionally he had had to manipulate the lump to maintain micturition. He denied any history of urolithiasis, urinary tract infection or similar disorder. He was married, with two children, and had a normal sexual life.

On examination he was febrile but otherwise fit. Blood biochemistry showed slightly elevated blood urea and serum creatinine. The bladder was not palpable. The external genitalia showed a coronal hypospadias with a stenosed meatus. There was a large palpable mobile stone approximately 3 cm in diameter a few millimetres below the meatus, partly visible through the meatus. Plain X-ray confirmed the presence of the stone (Fig.). Under local anaesthesia a simple meatomy was performed and the giant stone removed.

The stone was oval, smooth and whitish-yellow in colour and was broken after removal. Analysis showed calcium, magnesium, ammonium, carbonate and phosphatase. A subsequent IVU revealed normal function on both sides.

Comment

Primary urethral calculi usually occur in a congenital diverticulum (Marya *et al.*, 1977; Sinha and Rintoul, 1982). They do not obstruct the urinary flow unless infected and have been reported as being *in situ* for as long as 53 years. Bridges *et al.* (1982) described a urethral calculus lodged in the fossa navicularis but the stone was renal in origin. In our case it would seem that urinary stasis caused by congenital meatal stenosis may lead to the formation of a giant urethral stone.

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Requests for reprints to: B. M. S. Al Saleh, Department of Urology, Abu Dhabi Central Hospital, P.O. Box 233, Abu Dhabi, United Arab Emirates.

Giant Urethral Calculus in a Nine-year-old Girl

S. AHMED, *Department of Surgery, Adelaide Children's Hospital, North Adelaide, Australia*

Case Report

R.D., aged 9 years, presented with a 2-week history of pain, burning and frequency of micturition with intermittent haematuria. Urine examination showed 3520 polymorphs and 880 erythrocytes/cu mm, with a significant culture of *Streptococcus viridans*. There was no previous history of urinary problems but 4 years earlier she had suffered extensive flame burns necessitating hospitalisation for 6 months. Indwelling bladder catheters had been used at the time and further hospital admissions were necessary for the treatment of contractures.

No abnormalities were found on clinical examination. Radiological examination showed a large urethral calculus (Fig.). The stone was not visible on inspection of the introitus but, under general anaesthesia, it was just visible at the urethral meatus when proximal pressure was applied with a finger in the rectum. Urethral

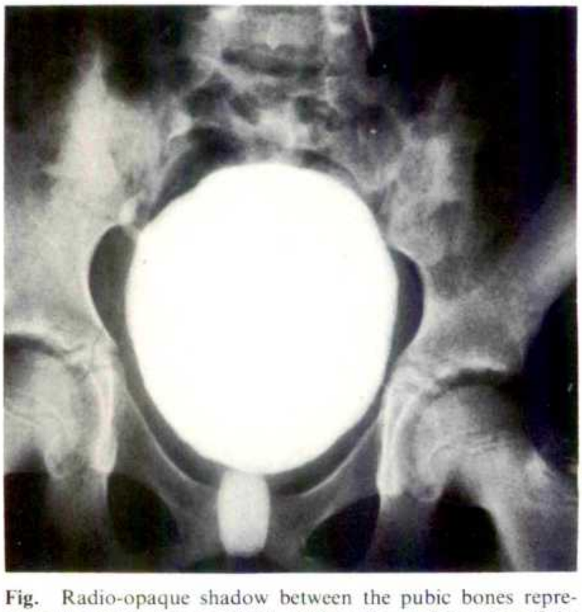

Fig. Radio-opaque shadow between the pubic bones represents the urethral stone which outlines the configuration of the female urethra. The upper urinary tracts were normal.

meatotomy, together with further proximal pressure, was sufficient to dislodge the stone. The child was discharged home the next day and because of suspicion of a meatal stricture the urethra was dilated 3 weeks later. There were no further urinary problems.

Biochemical investigation revealed no abnormality. The stone was 22 × 15 × 13 mm, hard, but with a smooth surface. Analysis showed that calcium phosphate was the major component together with carbonate and also magnesium.

Comment

Calculi are rarely seen in the urethra and the majority are seen in adults and in the male. Only 14 of 86 cases reported by Hussein (1973) were in children less than 14 years of age and there were no females in the entire series. A giant urethral calculus in such a young girl has, to my knowledge, not been reported previously. The radiological appearances in this case resembled those of a 30-year-old women reported by Hassan (1976). The latter patient presented more acutely, although there was a long history. It seems surprising that this young girl presented in a relatively insidious manner. As to the aetiology, it would seem that the calculus formed primarily in the upper tracts during the prolonged immobilisation from burns and migrated to the urethra, where it became impacted and enlarged.

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Requests for reprints to: S. Ahmed, Department of Paediatric Surgery, The Adelaide Children's Hospital, North Adelaide, South Australia 5006.

Granular Cell Myoblastoma of the Bladder

M. S. FLETCHER, M. AKER, J. T. HILL, J. P. PRYOR and W. F. WHIMSTER, *Departments of Urology and Pathology, King's College Hospital School of Medicine and Dentistry, London*

Case Report

A 48-year-old West Indian man presented with a short history of frequency of micturition and painless total haematuria. One year previously there had been a similar episode which was associated with bilateral loin pain and had been followed by the passage of a small calculus *per urethram*. Examination was unremarkable and urine microscopy revealed pus and red cells. Routine urine culture was sterile, as was culture for tubercle bacilli. No abnormality was seen on the intravenous urogram and at cystoscopy there were the appearances of cystitis on the bladder base, and these were biopsied. In addition, there was a nodule 2 cm in diameter above the left ureteric orifice which was resected (Fig. 1). Bimanual examination revealed no extrinsic mass. Twelve hours post-operatively the patient developed lower abdominal pain and tenderness and a cystogram confirmed an extravesical extravasation. Suprapubic exploration was performed and the prevesical space drained. The patient made a good recovery and no further abnormality has been noted in the bladder at subsequent cystoscopy. Microscopic examination of the resected nodule showed large polyhedral cells containing a granular esoinophilic cytoplasm and interspersed with a fine stroma (Fig. 2). The appearances were those of a granular cell myoblastoma. The areas of cystitis showed focal lymphocytic infiltration.

Comment

Granular cell myoblastomas are rare tumours which occur most often in the tongue and skin and only extremely rarely in the bladder; only six other cases have been reported (Mouradian *et al.*, 1974). Their histogenesis has been disputed and whilst electron microscopic and cytochemical evidence suggests the majority are of Schwann cell origin

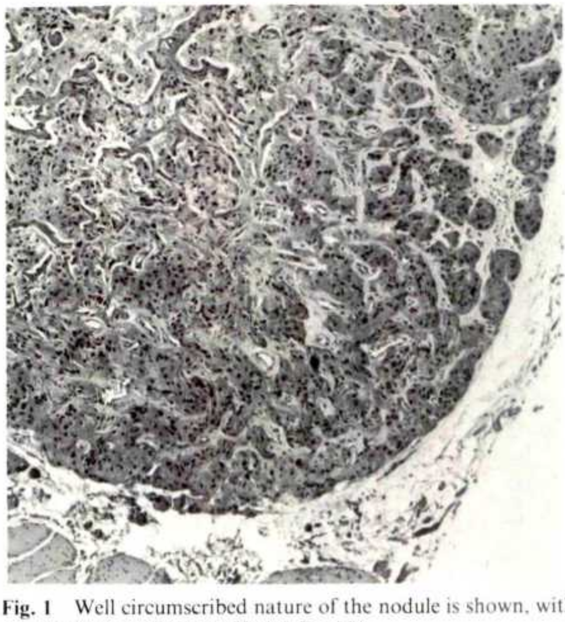

Fig. 1 Well circumscribed nature of the nodule is shown, with no overlying epithelium (H and E × 50).

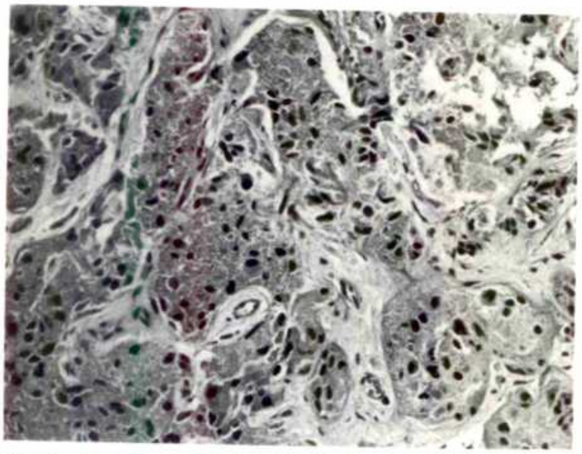

Fig. 2 Note large polyhedral cells interspersed with a fine stroma and containing granular cytoplasm (H and E × 125).

(Sobel *et al.*, 1973), a myogenous origin has been suggested by the finding of myofilaments within the tumour cells (Christ and Ozzello, 1971). Malignant variants have been reported but most of those occurring in the bladder are benign and may be treated by local excision (Mouradian *et al.*, 1974).

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Requests for reprints to: M. S. Fletcher, Thrombosis Research Unit, Department of Surgery, King's College Hospital Medical School, Denmark Hill, London SE5 8RX.

Nephrogenic Diabetes Insipidus and Obstructive Uropathy

I. A. AARONSON and J. WIGGELINKHUIZEN, *Department of Paediatric Surgery, Red Cross War Memorial Children's Hospital, Cape Town, South Africa*

Nephrogenic diabetes insipidus may produce gross dilatation of the upper urinary tract and bladder as a result of polyuria (Carter and Goodman, 1963).

The bladder contour, as seen on intravenous urography or cystography, is generally smooth or mildly sacculated. Gross trabeculation requires a search for an associated underlying bladder outflow obstruction.

Case Report

A 6-year-old boy with nephrogenic diabetes insipidus and progressive dilatation of the upper urinary tract was referred for review. In infancy, an ectopic ureterocele associated with a right duplex system had been unroofed and both right ureters brought to the surface as cutaneous end ureterostomies. His present intravenous urogram demonstrated disproportionate dilatation of the left upper tract and a markedly trabeculated bladder (Fig.). No outflow obstruction could be demonstrated on cystoscopy, but on video micturating cystourethrography the weak posterior wall of the unroofed ureterocele was clearly seen to bulge down during micturition and produce an obstructive lip at the bladder neck. No vesicoureteric reflux was seen. During voiding, his peak urinary flow was 7 ml/s. The affected portion of the trigone was excised and the right lower moiety of the ureter was reimplanted. The non-functioning upper moiety of the right kidney and its ureter were removed. Post-operatively, the functional capacity of the bladder has increased from 290 to 510 ml and his peak urinary flow to 17 ml/s.

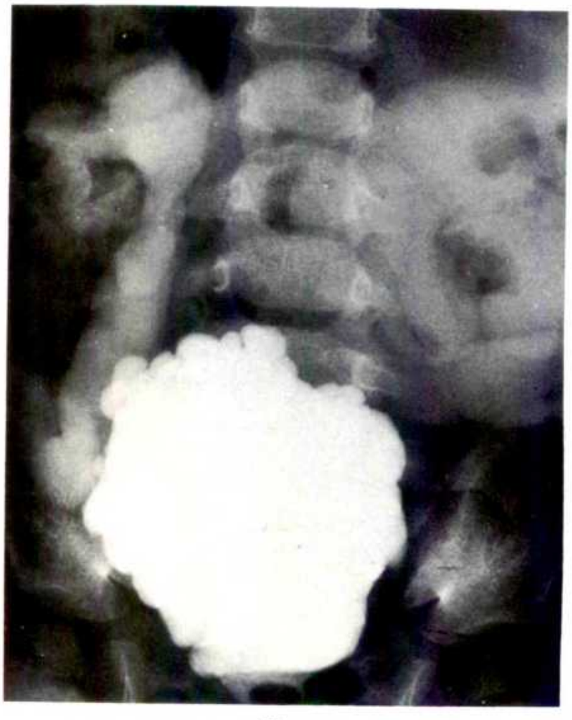

Fig.

Comment

The relentless polyuria of nephrogenic diabetes insipidus will considerably aggravate the changes in the urinary tract due to obstruction. A weak posterior wall of an ectopic ureterocele may on occasion be recognised on the pre-operative cystogram (Williams *et al.*, 1972). At operation, the quality of the ureterocele backing can only be assessed subjectively. Whenever a ureterocele is simply unroofed, the post-operative micturating cystourethrogram should be carefully examined to detect bulging of the affected portion of the trigone which may lead to bladder outflow obstruction.

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Requests for reprints to: I. A. Aaronson, Department of Paediatric Surgery, Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town 7700, South Africa.

Vascular lesion of the Verumontanum

G. R. SINCLAIR, CHRISTINE M. EVANS and P. KENCH,
Department of Urology, Flinders Medical Centre, Bedford Park, Australia

This report describes an unusual cause of acute retention in a male infant.

Case Report

A 2-year-old child presented with a 12-month history of intermittent difficulty in voiding, associated with strangury and temporary episodes of acute retention. Physical examination revealed no abnormalities and the haemoglobin, creatinine, urine analysis, X-ray of lumbosacral spine and intravenous urogram were normal. Cystourethroscopy was normal apart from a prominent verumontanum.

He was readmitted 2 months later with acute retention. A micturating cystogram (Fig. 1) showed a large filling defect in the prostatic urethra. At cystourethroscopy, a gross enlargement of the verumontanum was now obstructing the bladder neck and was easily resected. Post-operatively the child has voided normally.

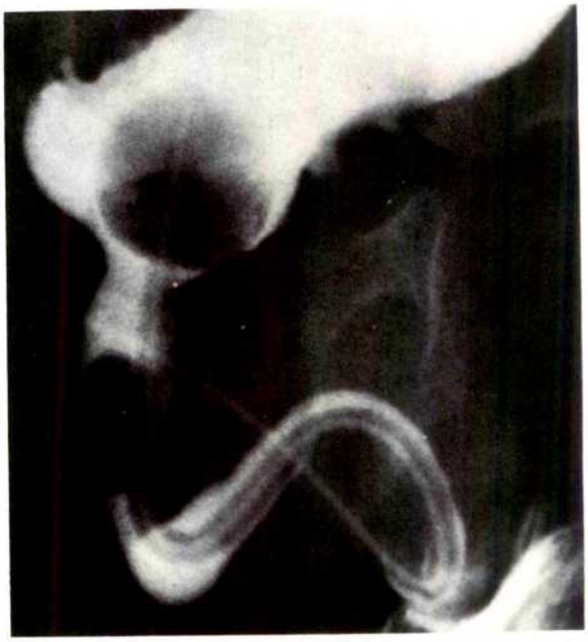

Fig. 1 Micturating cystogram. Large filling defect in prostatic urethra. Foley catheter in bladder.

Histology. Microscopically (Fig. 2) the lesion consisted largely of mature fibro-fatty tissue in which lay multiple abnormal vascular channels. These vessels had the structure of venules with relatively thin but muscular walls; many contained polymorphs. There was some local interstitial oedema and acute inflammation, but

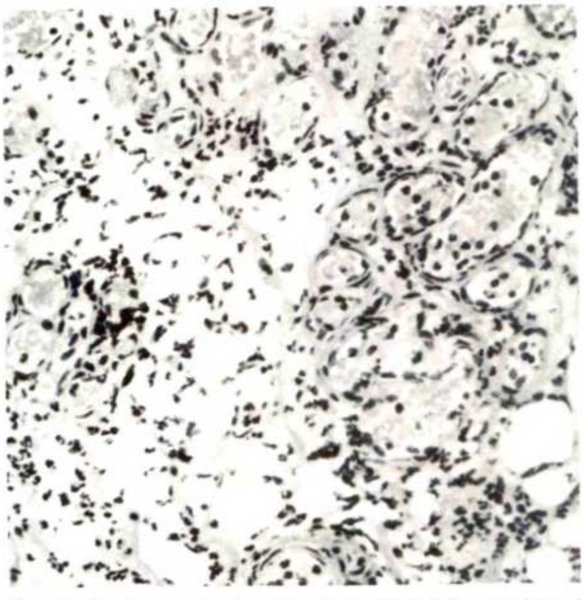

Fig. 2 Section of verumontanum. Denuded transitional epithelium seen overlying inflamed vascular lesion. (H and E × 175).

young fibroblasts or newly formed capillaries were not seen. Small numbers of acute inflammatory cells were present elsewhere in periurethral tissue. The surface was covered by transitional epithelium. The pathology is believed to represent an acutely inflamed vascular malformation.

Comment

The clinical picture correlates well with the pathology. Presumably the vascular enlargement of the verumontanum was prone to intermittent acute inflammatory changes, causing the short episodes of difficulty in voiding and the endoscopic change in size reported.

Requests for reprints to: G. R. Sinclair, Department of Urology, Flinders Medical Centre; Bedford Park, South Australia 5042.

Points of Technique

Closure of Urethral Fistula by Rhombic Flap

A. K. SINGH and R. CHANDRA, *Postgraduate Department of Plastic Surgery, King George's Medical College, Lucknow, India*

Urethral fistulas are a known complication of hypospadias surgery. The incidence of fistula formation varies from centre to centre and according to the operative technique used, but an average rate of 8 to 20% has been reported (Horton, 1973). Repair of these fistulas is often a difficult problem, for many patients have a history of multiple operations. Several procedures have been used, ranging from simple closure, Y-V advancement (Saad *et al.*, 1980) and rotation of a local flap (Roberts, 1982) to the use of a tubed pedicle in intractable cases.

We used a rhombic flap to provide a two-layered closure of urethral fistulas in four patients, each of whom had already been subjected to more than one attempt at closure. Local anaesthesia was used and the risk of distal obstruction was avoided by passing a catheter of appropriate size. The patients made a satisfactory recovery and were discharged 3 to 5 days post-operatively.

Technique

A diamond-shaped incision is made, enclosing the fistulous opening, with the long axis lying parallel to the penis (Fig. 1A). The skin within the rhombus is excised, taking care not to damage the mucosa. This is facilitated by injecting a local anaesthetic in the subcutaneous plane. The mucous layer is closed longitudinally with continuous 5/0 chromic catgut inverting sutures. A proximally based rhombic flap is constructed over the defect (Limberg, 1966). The shorter diagonal is extended in one direction, equal to its length. The third side of the flap is created by making an incision (from the end of the preceding one) parallel and equal to one of the sides of the defect. The flap is undermined and elevated (Fig. 1B). Care is taken to achieve absolute haemostasis prior to tranposition and stitching of the flap. No secondary defect remains. The patient is allowed to pass urine *per urethram* and encouraged to void frequently. Antibiotics and urinary alkalisers are administered routinely.

To prevent recurrence, the following precautions should be observed:

(i) The closure should be in two layers.
(ii) The suture lines should not overlap.
(iii) Haematoma formation should be meticulously avoided.
(iv) No infection should occur.

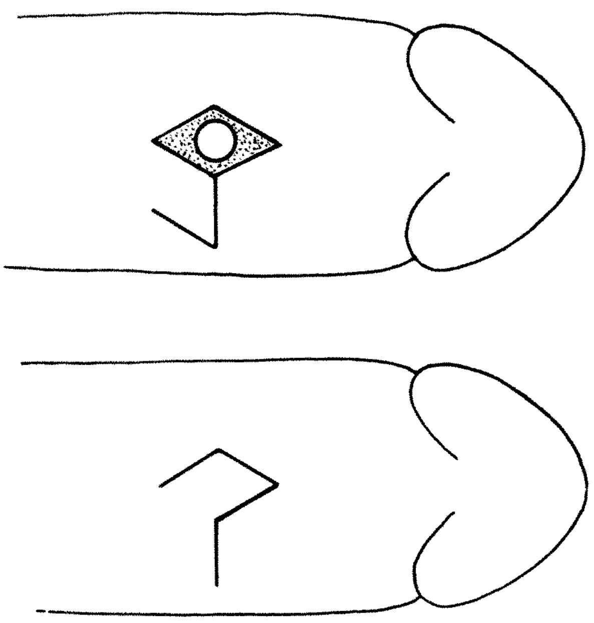

Fig. 1(A) Markings of the flap. (B) Appearance after transposition.

(v) Catheterisation should be avoided if possible as it leads to periurethritis and increases the risk of fistula formation.

Local flaps have previously been used for the closure of urethral fistulas. A rhombic flap seems an acceptable alternative and fulfils all essential prerequisites. It is a safe procedure, producing no tension on the flap and no secondary defect. The results in our patients have been satisfactory and there has been no recurrence of the fistulas.

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Requests for reprints to: A. K. Singh, 108/4, Nripendra Sanyal Road, Ruby House, Model Houses, Lucknow-226001, India.

Ureteroscopic Placement of Ureteric Catheter for Obstructing Calculus

D. H. BAGLEY, J. L. HUFFMAN and E. S. LYON,
Department of Surgery, University of Chicago, Chicago, USA

Ureteroscopy and ureteropyeloscopy have rendered the ureter accessible for direct endoscopy. The technique and value of uteteroscopic placement of a ureteric catheter in a patient with a totally obstructing proximal ureteric calculus is described. Use of the rigid ureteropyeloscope for placement of a ureteric catheter in selected cases is a valuable technique for the urologist.

The ureter has been inaccessible to endoscopy until the recent development of ureteroscopic (Lyon *et al.*, 1978, 1979) and ureteropyeloscopic (Huffman *et al.*, 1982; Perez-Castro Ellendt and Martinez-Pineiro, 1982) techniques. Ureteric lesions have previously been studied, manipulated or bypassed by blind intraureteric techniques. Circumstances may require that a ureteric calculus be bypassed by a catheter beyond the obstructing stone into the proximal urinary tract to provide drainage. Problems with the blind technique may arise if the calculus is tightly adherent to the ureteric wall and a catheter will not pass, or if the ureter is perforated by the catheter near the obstruction. The combination of ureteroscopy with ureteric catheterisation can now provide adequate drainage in a patient with an obstructing ureteric calculus.

Case Report

A 57-year-old female was admitted for treatment of bilateral staghorn calculi. The patient was massively obese and was afebrile at the time of admission. Serum creatinine was 2.8 mg/dl. The other blood chemistries and haematological evaluation were within normal limits. A radiograph of the abdomen showed a large staghorn calculus filling the collecting system of the right kidney and multiple calculi filling portions of the collecting system on the left. A renal scan demonstrated decreased perfusion and function bilaterally with a ratio of approximately 9:1, right to left. A retrograde ureteropyelogram demonstrated a totally obstructing calculus in the proximal left ureter.

In order to drain the left kidney pre-operatively, an attempt was made to pass a ureteric catheter but this proved impossible despite repeated attempts with different catheter designs (Fig. 1). Ureteroscopy was therefore

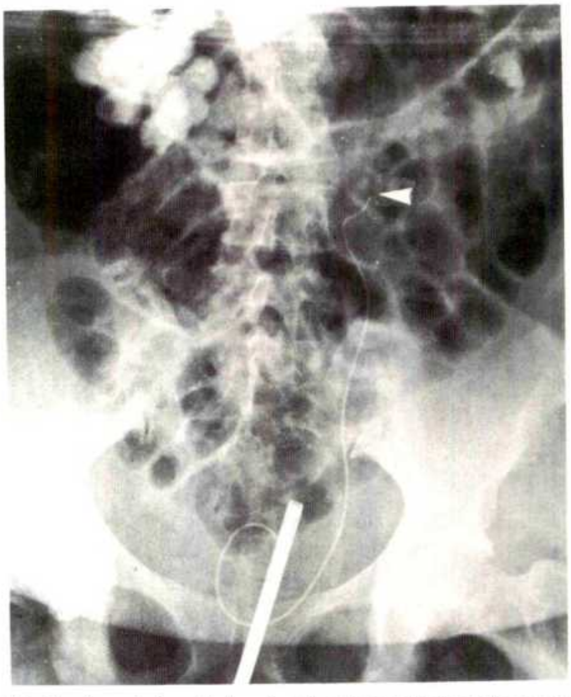

Fig. 1 A ureteric catheter placed cystoscopically will not pass the calculus obstructing the proximal ureter (arrow).

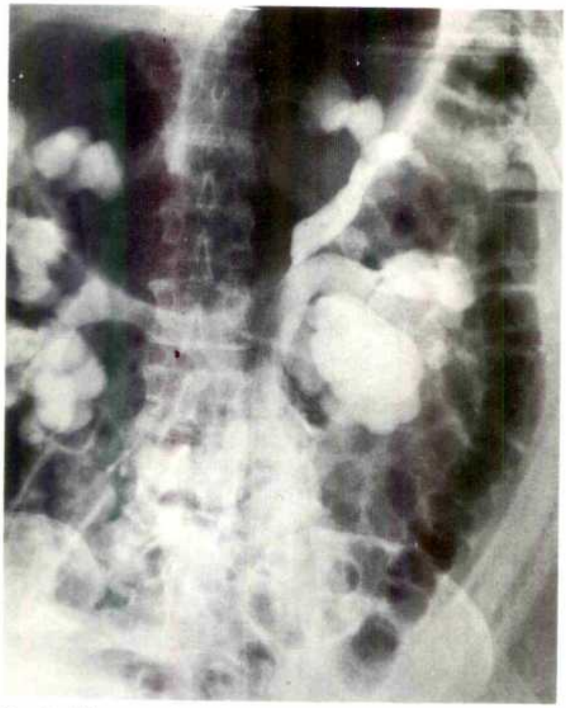

Fig. 2 The ureteric catheter has been replaced within the collecting system under direct vision and the injection of contrast indicates its proper placement.

performed to see the calculus and place the catheter. After dilatation of the intramural ureter the ureteropyeloscope (Richard Wolf, Medical Instrument Corporation, Rosemont, USA) was passed to the level of the calculus, which was tightly adherent to the ureteric wall, nearly circumferentially. A 5F whistle tip catheter was directed towards the periphery of the stone near the ureteric wall and advanced. A radiograph taken with injection of contrast through the catheter demonstrated contrast outside the collecting system. The catheter was then withdrawn and again passed under direct vision between the stone and the ureteric wall at a second position. A rapid flow of urine was obtained from the catheter. A retrograde ureteropyelogram performed through the catheter then demonstrated the upper collecting system (Fig. 2). The catheter was maintained on drainage. The patient subsequently underwent left ureterolithotomy and nephrolithotomy with recovery of function in that kidney.

Comment

The rigid ureteropyeloscope can be safely passed within the ureter to observe, biopsy and manipulate intrauteric lesions and calculi (Huffman *et al.*, 1982). This case history demonstrates another use for the instrument. In this patient, if the kidney could not be drained endoscopically, an operative procedure would have to be performed on the kidney without accurate knowledge of the intrarenal collecting system or the potential for functional recovery. Decompression by percutaneous nephrostomy was considered but was not attempted because of the patient's massive obesity.

With the calculus under direct vision within the ureter, it was possible to pass the catheter towards the point at which the ureter appeared to be least adherent to the calculus. When the perforation occurred, the catheter could be withdrawn easily and repositioned without risk of passing through the same point of perforation. Such accuracy in repositioning the catheter would be impossible without direct visual control. Use of the rigid ureteropyeloscope to place a ureteric catheter beyond a totally obstructing ureteric calculus is a valuable technical addition for the urologist.

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Pérez-Castro Ellendt, E. and Martinez-Piñeiro, J. A. (1982). Ureteral and renal endoscopy—a new approach. *European Urology*, **8**, 117-120.

Requests for reprints to: D. H. Bagley, Jr., Department of Urology, Jefferson Medical College, 1025 Walnut Street, Room 1112/College, Philadelphia, PA 19107, USA.

Technical Modifications of Anderson Hynes Pyeloplasty for Congenital Pelviureteric Junction Obstruction

P. A. McLEAN, W. F. GAWLEY and T. P. GOREY,
Department of Urology, Jervis Street and Richmond Hospitals, Dublin, Eire

Of 100 cases of pelviureteric junction obstruction seen over a 10-year period, 55 were treated by Anderson Hynes pyeloplasty (Anderson and Hynes, 1949). Details of ureteric vasculature and our method of flap approximation are described.

Wise case selection and meticulous technique make pyeloplasty one of the most rewarding procedures in urology. Our technique is based on a series of 55 consecutive and successful Anderson Hynes pyeloplasties. We direct attention to the important areas of ureteric vasculature and the method of flap overlap and mucosal approximation.

The pelviureteric area receives blood from a branch of the renal artery that forms a plexus on its surface and gives off several branches which descend posteriorly in the attached mesentery. The ureteric mesentery, which attaches the ureter to the posterior abdominal wall, must be carefully preserved. The ureter is retracted with its mesentery intact by means of a fine catgut suture in its anterior wall (Fig. 1). The use of retractor slings in this area should be avoided.

To avoid overlapping and puckering at the apex of the anastomosis we incise the ureter laterally (Fig. 2) and tailor the apex of the pelvic flap to fit comfortably into the open ureter.

To approximate mucosa accurately can be difficult because the apex of the anastomosis tends to invert and we use a U-shaped everting suture (Fig. 3) which results in an edge-to-edge closure (Fig. 4).

We consider nephrostomy tubes or stents unnecessary since post-operative drainage has been minimal. The average length of follow-up in this series was 7 years and results are considered good, with the elimination of symptoms and non-progression of the hydronephrosis. Such results compare favourably with those of other series (Culp, 1967; Karlberg, 1976).

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Requests for reprints to: P. A. McLean, Department of Urology, Jervis Street Hospital, Dublin, Eire.

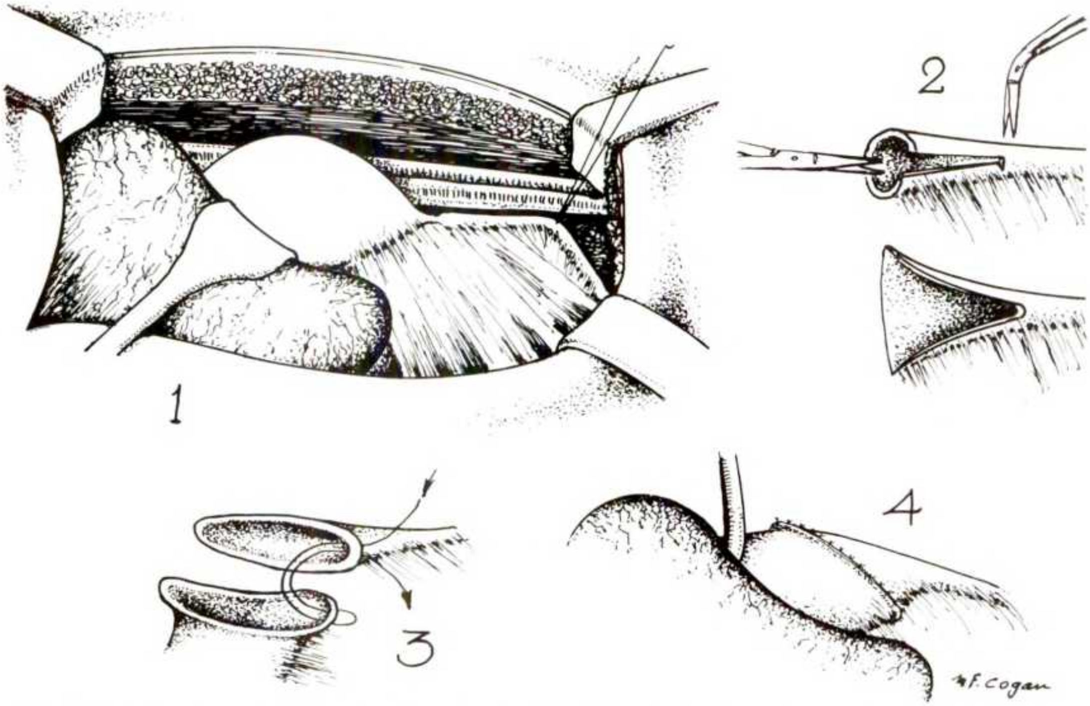

Fig. 1 Ureteric mesentery. **Fig. 2** Tailoring of ureter. **Fig. 3** Everting apical suture. **Fig. 4** Accurate closure.

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Notices

British Association of Urological Surgeons

President: Professor J. P. Blandy, DM, MCh, FRCS, FACS

Annual Meeting: Eastbourne, 9-12 July 1985

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Edinburgh Urological Festival 1985

Edinburgh, 28-30 August 1985

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Shackman Travelling Fellowship

The Fellowship for 1985 has been awarded to Mr A. C. Buck, Cardiff, to enable him to work in Munich University on the subject of "The influence of prostaglandins and their inhibitors on calcium transport in the kidney."

Shackman Travelling Fellowships 1986

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited Training Programme in Urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent University status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the UK or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to Urology or to Renal Transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1985.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

London Hospital Medical College: Department of Urology

Practical Endoscopic Urology: 21-22 March 1985

Further information on the above course may be obtained from: B. G. Daley, Postgraduate Centre, London Hospital Medical College, 47 Turner Street, London E1 2AD.

Symposium on Investigating the Urinary Tract in Children

Selwyn College, Cambridge, 19-21 June 1985

The Cambridge summer meeting in residence is a regular event for interested radiologists and clinicians. About half of the programme is reserved for discussion between speakers and audience. Inclusive cost £105.

Further details from: Professor T. Sherwood, Department of Radiology, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

Second Germ Cell Tumour Conference

Leeds, 15–19 April 1985

Further particulars from: W. G. Jones, Department of Radiotherapy, Cookridge Hospital, Leeds LS16 6QB.

Urology Course

University of Glasgow. 1-3 April 1985

A 3-day course particularly for urological trainees and for consultants with an interest in the specialty. A variety of topics will be covered by formal lectures and there will be a session on Practical Aspects of Urology, including demonstrations. The registration fee is £110.

Further particulars from: Mrs Elizabeth A. McPherson, Administrative Assistant, West of Scotland Committee for Postgraduate Medical Education, University of Glasgow, Glasgow G12 8QQ. Telephone: 041-339 8855, Ext. 7274, *or* Mr D. Kirk, Urological Department, Royal Infirmary, 16 Alexandra Parade, Glasgow, G31 2ER. Telephone: 041-552 3535, Ext. 5493.

Urological Days of Necker 1985

Paris, France. 14-16 March 1985

The topics will be:

(1) Embryonal tumours of the renal parenchyma.
(2) Intra-operative imaging of the kidney and upper urinary tract.

Further particulars from: Professor J. Cukier, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

European Nuclear Medicine Congress 1985

London. 3-6 September 1985

Further particulars from: Congress Secretariat, Institute of Nuclear Medicine, Middlesex Hospital, Medical School, Mortimer Street, London W1N 8AA.

Fourth Congress of the European Society for Urological Oncology and Endocrinology

Amsterdam, The Netherlands. 24-27 April 1985

Further particulars from: Professor H. J. de Voogt, Department of Urology, Free University Hospital, P.O.B. 7057, 1007 MB Amsterdam, The Netherlands.

20th Congress of the International Society of Urology

Vienna, Austria. 23-28 June 1985

Topics

1. Ultrasound in diagnosis and treatment.
2. Emergency treatment of traumatic lesions in the urinary tract.
3. Bladder tumours: prognosis and treatment.

Round Tables

1. Laser in urology.
2. Treatment of testicular tumours.

Note: Only members of the International Society of Urology may participate in the Congress, but members may sponsor one colleague who wishes to attend.

Further particulars from: Secretariat, XXth Congress of the International Society of Urology, c/o Vienna Academy of Medicine, Alser Strasse 4, A-1090 Vienna, Austria.

12th Meeting of the International Study Group for Steroid Hormones

Rome, Italy. December 1985

The main topics of the meeting will be:

1. Steroid peptide interaction
2. Sex hormone antagonists.
3. Intratissular steroids and hormone dependent corneu.

Deadline for presentation of abstracts: 30th June 1985.

Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma, viale del Policlinico, 00161 Rome, Italy.

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Book Reviews

Case Presentations in Renal Medicine. By R. A. Coward, C. D. Short and N. P. Mallick, Pp. xiv + 172. Sevenoaks: Butterworths. 1983. Price £5.95.

This book was written for doctors studying for higher examinations, particularly the MRCP, and the authors hope that it will also be of value to students. The aim of the book is to demonstrate the way in which patients with renal disease present to physicians, how they are investigated, and what treatment regimes may be employed. I think that the authors achieve all of their objectives admirably in a concise, moderately priced book.

The book is based on the description of 50 cases seen by the authors with, at the end of each case description, a few questions followed by comments and discussion concerning the condition illustrated. There is a topic section with brief descriptions of methods of investigation and important aspects of management of patients with renal disease.

This is a stimulating book with an impressive amount of information brought out by the description of cases and comments. Most varieties of renal disease are illustrated by the cases presented. While this method of learning may not appeal to all, there are distinct advantages in illustrating conditions using real cases.

The topic section at the end perhaps suffers as a result of its brevity. The section on imaging in renal disease is already a little outdated, with insufficient emphasis on ultrasound, and little information on the hazards of high dose intravenous urography. However, there are useful descriptions of important aspects of diagnosis and management, particularly sections on how to insert a peritoneal dialysis cannula, and a description of the complement pathway in the context of glomerular disease.

There is also a useful description of the physical signs in the face in renal disease and at the end of the book there is a good index.

This book would be of great value to doctors studying for membership and also to medical students. While most of the contents are perhaps not strictly relevant to surgical practice, there is no doubt that surgeons, particularly urologists, would benefit from reading this book.

CO_2 Laser Surgery. By I. Kaplan and S. Giler. Pp. 206. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1984. Price DM 198,--; approx. US $76.90.

This small, well illustrated handbook records the clinical experience of the Department of Plastic and Maxillofacial Surgery in Tel-Aviv, Israel, in CO_2 laser surgery. A rather brief introduction to the equipment is followed by the indications for the technique, emphasising the use of the laser as a "bloodless scalpel". Good examples of excisional surgery are shown using pre- and post-operative photographs, but the accompanying text is very limited. There is, however, very little to tempt the practising urologist here, particularly as this form of laser light cannot at present be directed down a flexible fibreoptic attachment, unlike the YAG laser. The only examples of non-endoscopic urological procedures included are block dissection of the inguinal nodes and excision of an advanced locally spreading seminoma of testis. With these reservations, the book is well set out, clearly shows the results that can be achieved, and would therefore prove useful to those interested in the field.

Varicocele and Male Infertility II. Edited by M. Glezerman and E. W. Jecht. Pp. 122. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1984. Price DM 38,--; approx. US $14.80.

This brief volume contains the papers given at an International Symposium on Varicocele which was held at the Second International Congress of Andrology in 1981. It is a valuable reference work for those interested in the relationship between varicocele and infertility and contains a useful introduction to the newer methods of diagnosis and percutaneous treatment of varicocele. The muddied waters have clarified little in the subsequent years.

Book Received

Contributions to Nephrology, Volume 37: Risk Profiles in Clinical Nephrology. Edited by G. Buccianti. Pp. x + 199. Basel: Karger. 1984. Price SFr. 90.--; DM 108.--; US $54.00.

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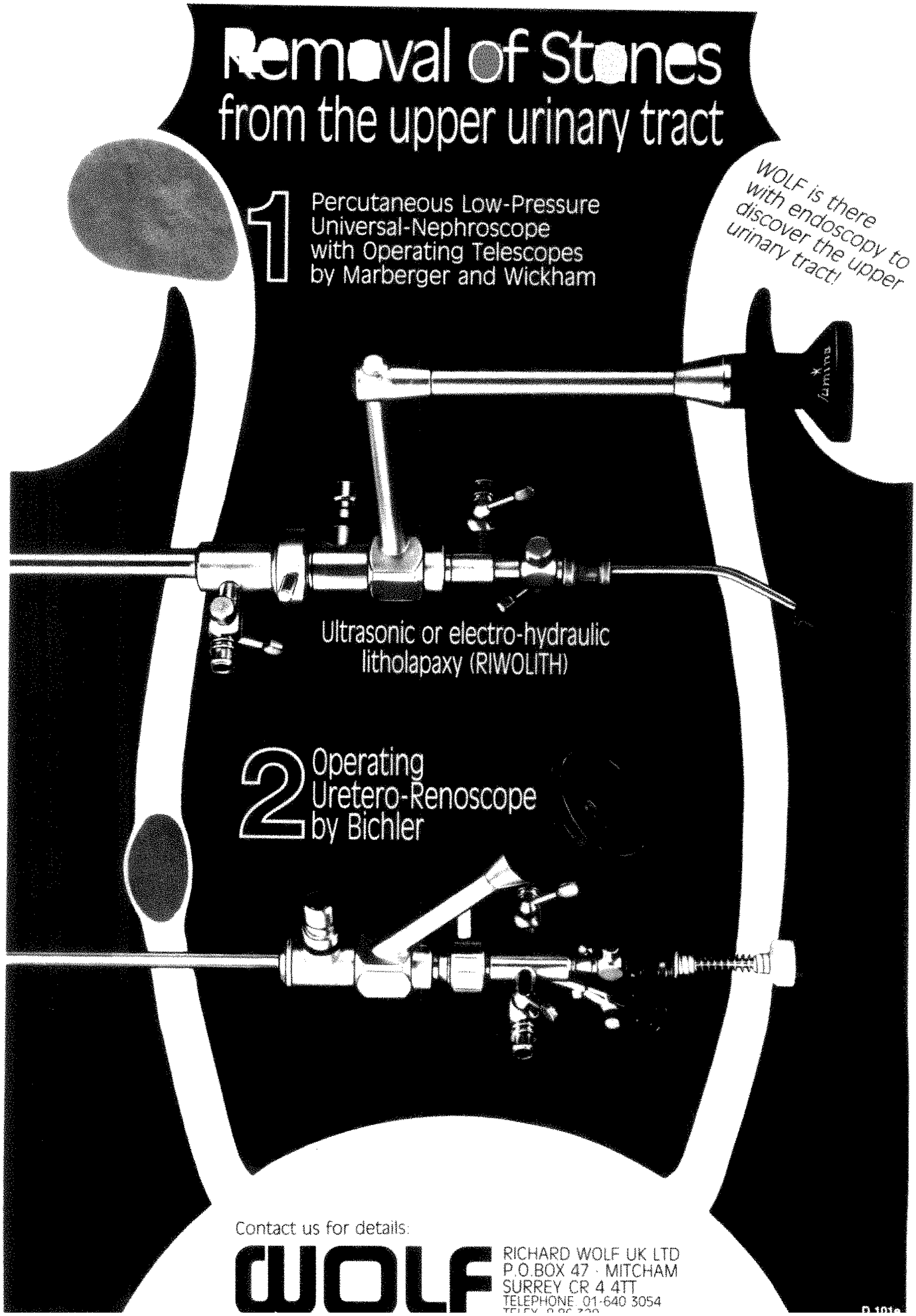

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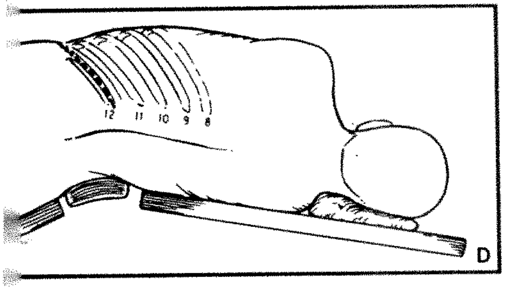

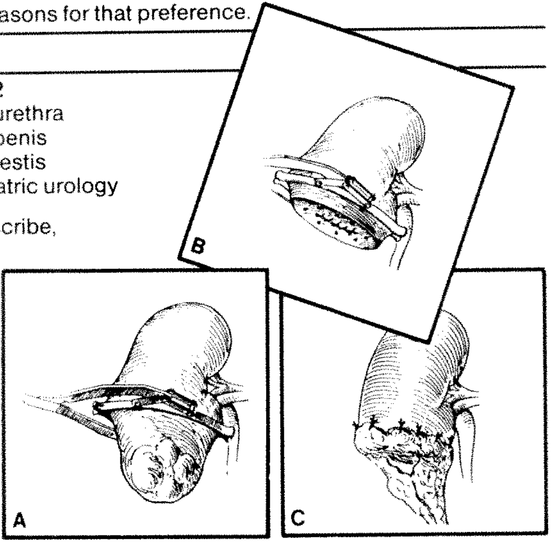

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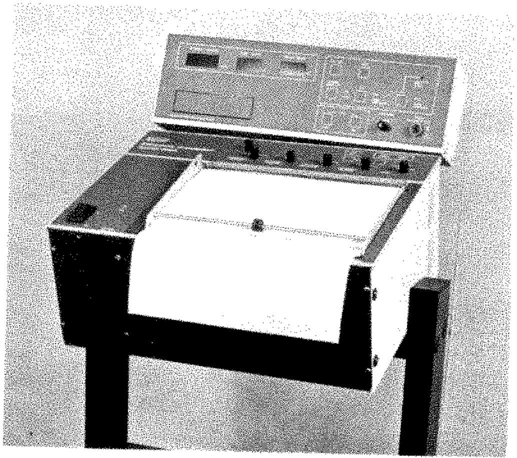

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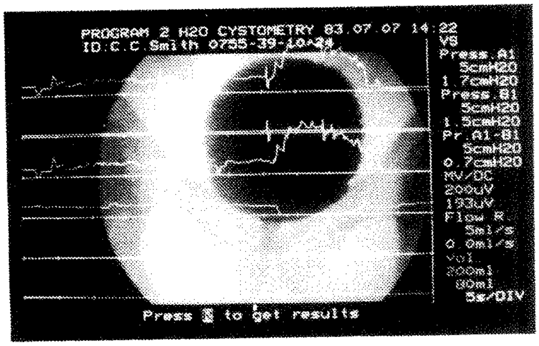

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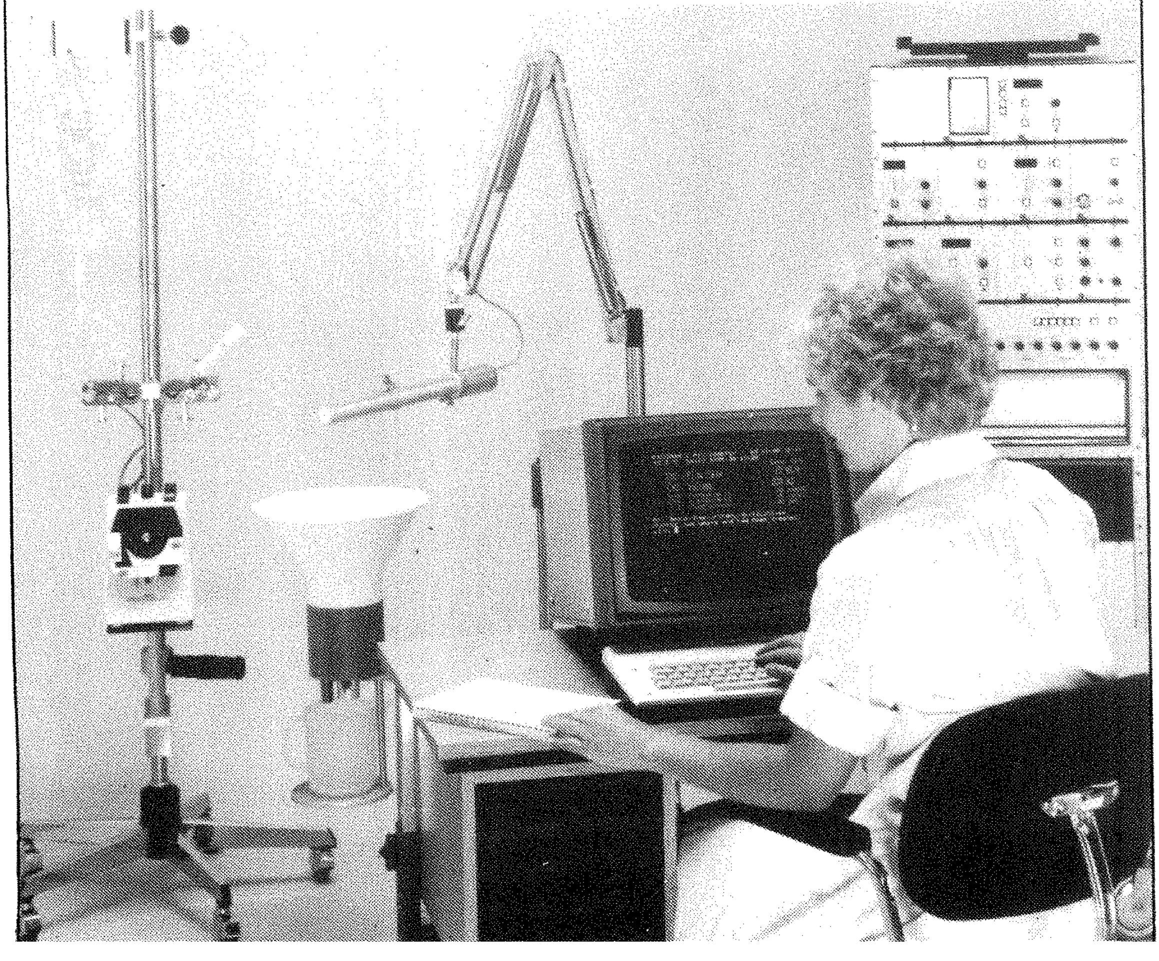

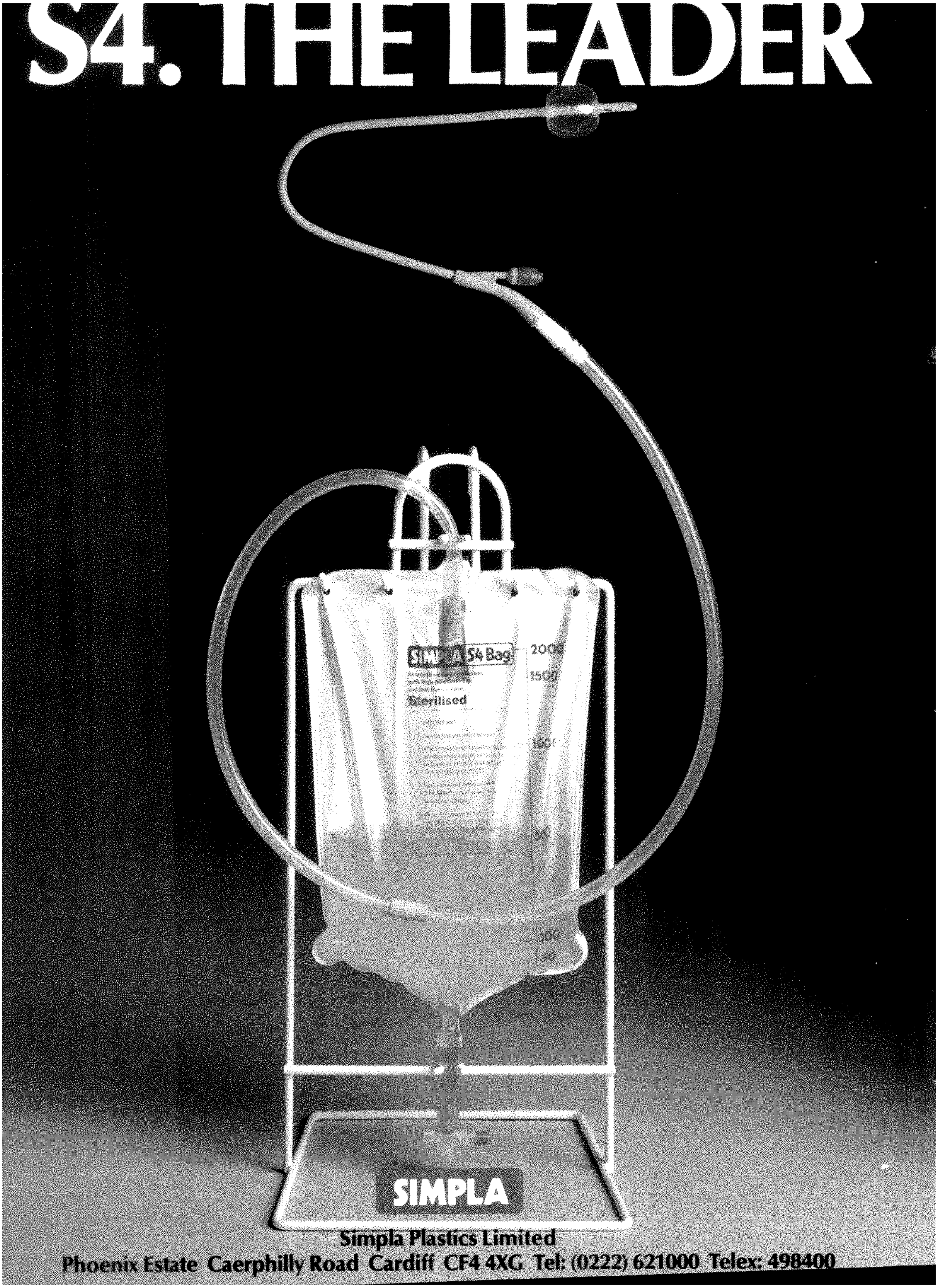

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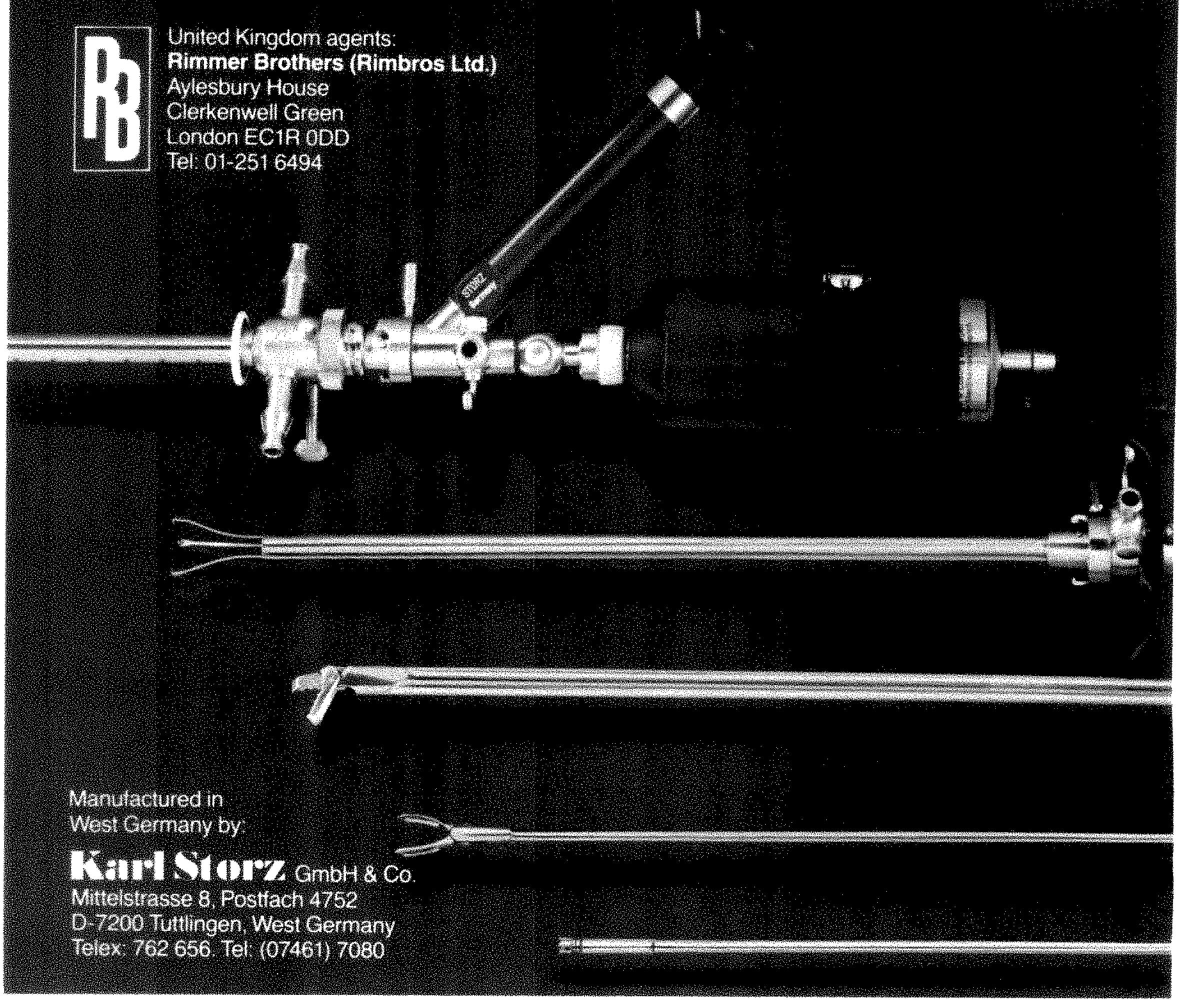

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A Comparison of Diuresis Renography, the Whitaker Test and Renal Pelvic Morphology in Idiopathic Hydronephrosis

E. W. LUPTON, D. RICHARDS, H. J. TESTA, S. A. GILPIN, J. A. GOSLING and R. J. BARNARD

Departments of Urology and Radiology, University Hospital of South Manchester; Department of Anatomy, Manchester University; Department of Nuclear Medicine, Royal Infirmary, Manchester

Summary—Diuresis renography and the Whitaker test are established methods of diagnosing obstruction in dilated renal pelves. These techniques have been compared in 36 patients with radiologically demonstrated idiopathic hydronephrosis and evaluated, where possible, against renal pelvic morphological features. The agreement between the results of the tests was as follows: diuresis renography/Whitaker test 67%; diuresis renography/renal pelvic morphology 74%; Whitaker test/renal pelvic morphology 58%. Both diuresis renography and the Whitaker test are indicated in some cases of idiopathic hydronephrosis.

The investigation of equivocal upper urinary tract obstruction has been one of the most hotly debated topics in urology during the past 10 years. Idiopathic hydronephrosis remains a common clinical problem and a decision concerning the benefits and timing of surgery in individual cases has been considerably aided by newer diagnostic techniques. Two "front-runner" tests have emerged as the most efficient means of distinguishing obstructive from non-obstructive dilatation, namely diuresis renography (O'Reilly *et al.*, 1978) and the Whitaker test (Whitaker, 1973). Both have advantages and disadvantages in making this important distinction and neither can therefore be regarded as a "gold standard" against which other investigations should be evaluated.

The morphological features of the dilated upper urinary tract are probably the best determinant of the presence or absence of obstruction before renal function starts to deteriorate. Gosling and Dixon (1978) described characteristic histochemical and structural changes in obstructive idiopathic hydronephrosis. In cases of renal pelvic dilatation believed to be non-obstructive the morphology was the same as in normal controls (Lupton *et al.*, 1979).

This report therefore compares diuresis renography with the Whitaker test in idiopathic hydronephrosis. Where possible, that is when specimens were provided per-operatively, both tests have been evaluated against renal pelvic morphology.

Patients and Methods

Thirty-six patients with unilateral urographically demonstrated idiopathic hydronephrosis were assessed. All had diuresis renography which was performed using mainly a gamma camera-computer system, intravenous ^{123}I Hippuran in a dose of 0.5 mBq/kg and intravenous frusemide (0.5 mg/kg) (O'Reilly *et al.*, 1979) (Fig. 1). An equivocal result was represented by an excretion pattern with a slope between response IIIA and IIIB. Kidneys with such a pattern could sometimes be recategorised as obstructive or non-obstructive by modifying the diuresis renogram, administering the frusemide 15 min before the start of the test (English *et al.*, unpublished data). An additional group consisted of the kidneys with poor function.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

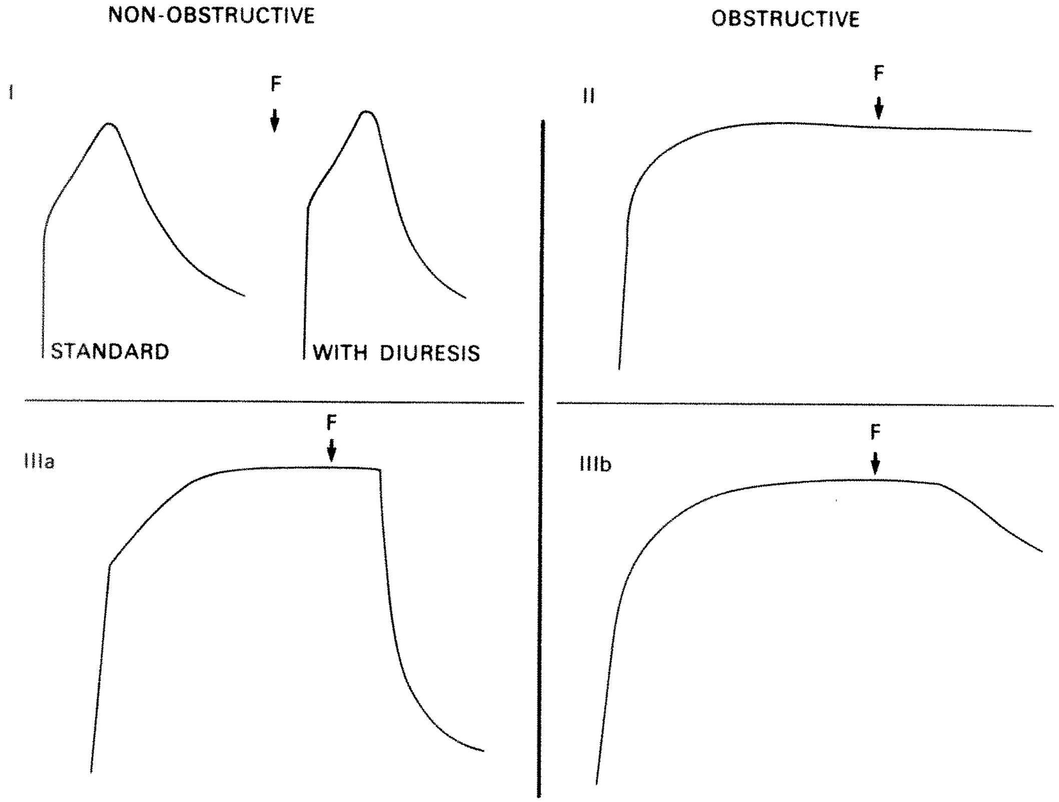

Fig. 1 Diuresis renography: non-obstructive—groups I and IIIa; obstructive—groups II and IIIb; F = frusemide administered.

The Whitaker test was attempted in all 36 patients and carried out in standard fashion using the following equipment: Braun syringe pump, 3-way tap, Statham pressure transducers, Hewlett Packard electronic and chart recording equipment and manometer tubing. Twenty-seven studies were performed by percutaneous puncture of the affected renal pelvis under ultrasound and/or X-ray control. Seven pressure-flow studies were carried out per-operatively by direct needle puncture of the renal pelvis and in two patients a pre-implanted nephrostomy tube was used for access. The renal pelvis was perfused at a constant flow rate of 10 ml/min using contrast medium or saline and the pressure in the bladder was recorded simultaneously with that in the pelvicaliceal system. The relative renal pelvic pressure at equilibrium or at discontinuation of a study with a rising curve was determined (Whitaker, 1973). The following criteria were used: obstructive > 22 cm H_2O, equivocal 15-22 cm H_2O and non-obstructive < 15 cm H_2O (Fig. 2).

The morphological features of specimens of the renal pelvis removed at operation were assessed independently of the renograms and pressure-flow studies. The specimens were delivered fresh from the operating theatre and, after freezing, cryostat sections were prepared and examined by light microscopy and tissue cholinesterase techniques. The abnormal morphological changes characteristic of obstruction are well established (Gosling and Dixon, 1978) and include marked collagen and elastin infiltration between and within muscle bundles as well as reduced or absent smooth muscle cholinesterase. Examples of normal and abnormal features are shown in Figure 3.

Results

Diuresis renography was compared with the Whitaker test in 36 cases (Table 1). The excretion response to diuresis could not be assessed in five patients with poor function on renography because the uptake of the radiopharmaceutical was too slow. A direct comparison between the diuresis renogram and the Whitaker test was therefore precluded in these cases. The Whitaker test was unsuccessful in five instances: in three because of extravasation producing either severe pain or a low renal pelvic pressure, in one because renal pelvic

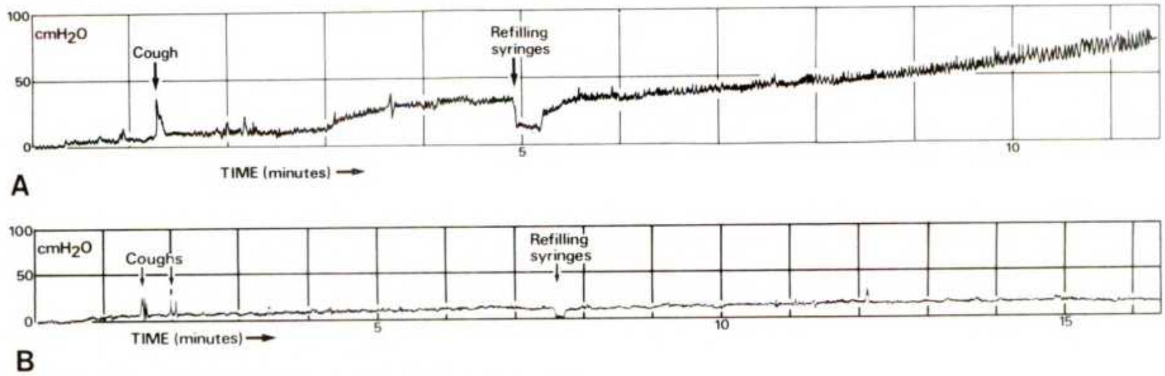

Fig. 2 The Whitaker Test: (A) Obstructive. (B) Non-obstructive.

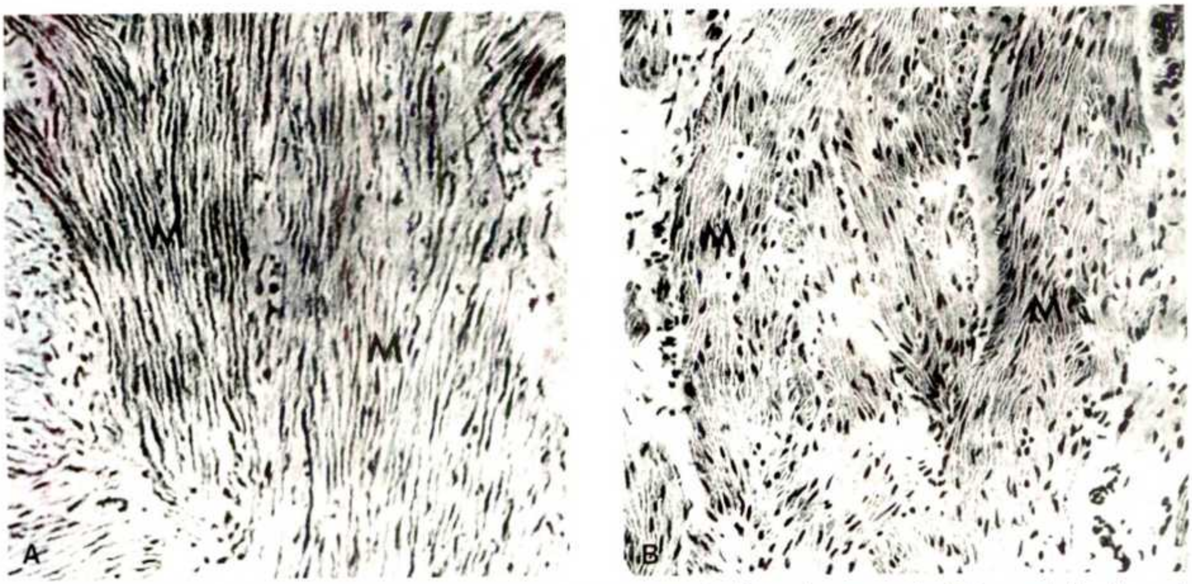

Fig. 3 Renal pelvic morphology: (A) Obstructive—excessive amounts of collagen between and within muscle bundles and distortion of muscle arrangement. (B) Non-obstructive—normal distribution of connective tissue around muscle bundles. M = muscle.

puncture failed and in one because the catheter slipped out after an initially successful placement. The results of the two tests were comparable in 27 patients and there was agreement in 18 (67%).

Considering the comparison between diuresis renography and renal pelvic morphology (Table 2), it is notable that all five poorly functioning kidneys had abnormal morphological features, and this

Table 1 Comparison of Diuresis Renography with the Whitaker Test (36 Kidneys)

		Whitaker test			
		Obstructed	*Non-obstructed*	*Equivocal*	*Unsuccessful*
Diuresis renogram	obstructed	11	8		2
	non-obstructed		5		1
	equivocal		1	2	1
	poor function	1	3		1

Table 2 Comparison of Diuresis Renography with Renal Pelvic Morphology (24 Kidneys)

		Renal pelvic morphology		
		Abnormal	*Normal*	*Equivocal*
Diuresis renogram	obstructed	11	3	1
	non-obstructed		1	
	equivocal	1		2
	poor function	5		

Table 3 Comparison of the Whitaker Test with Renal Pelvic Morphology (19 Kidneys)

		Renal pelvic morphology		
		Abnormal	*Normal*	*Equivocal*
Whitaker test	obstructed	7	1	1
	non-obstructed	5	3	
	equivocal	1		1

confirms the clinical impression that the impaired function was the end-result of obstruction. Because it was impossible to obtain a renogram response to the diuretic these five cases were excluded from the comparison, which was therefore restricted to 19 cases. There was an agreement in 14 (74%). The Whitaker test results were evaluated against renal pelvic morphological findings in 19 patients. It is noteworthy that there were five kidneys with non-obstructive pressure-flow studies in which the morphology was found to be abnormal. There was agreement between the results of the two tests in 11 instances (58%).

Discussion

There have been sporadic reports comparing diuresis renography with the Whitaker test in the study of upper urinary tract dilatation. Koff *et al.* (1980) found disagreement between the results of the tests in 1 of 14 cases. Whitaker and Buxton-Thomas (1984) found only a 61% correlation between the two techniques in 32 patients. Included in their series were six cases with non-obstructive diuresis renograms and obstructive perfusion studies.

The present series has shown a 67% overall correlation between diuresis renography and the Whitaker test, rather lower than might be expected for two techniques which assess the excretion characteristics of the renal pelvis. However, each test achieves this assessment by measuring different parameters and it is not surprising that there are some discrepancies. Diuresis renography is at a potential disadvantage because neither the pressure within an affected kidney nor the flow rate from it is known. Nevertheless, it is a more physiological test and attempts to assess how an individual kidney handles a fluid load without the invasive interference of a renal pelvic needle. It is notable that in our series there were no instances of non-obstructive diuresis renograms associated with high pressures in the perfusion study. This is probably because we are very strict in categorising a kidney as non-obstructive on renography, requiring a precipitous fall in the tracing in response to the diuretic. We would accept that there are some diuresis renogram tracings which simulate obstruction due to poor function in the affected kidney. The experienced observer, however, is usually able to distinguish between these entities. Dilated pelvicaliceal systems with highly compliant walls may also have an obstructive pattern on renography but low pressures on perfusion.

The concept that a pressure rise is an essential feature of an obstructed upper urinary tract has recently been questioned (Holden *et al.*, 1984). Furthermore, Djurhuus *et al.* (1976) have shown that obstruction as evidenced by disturbed impulse conduction (measured with renal pelvic EMG) may be associated with low pressures within the pelvicaliceal systems of hydronephrotic kidneys. This may be one of the explanations for obstructive diuresis renograms associated with low pressures recorded during the Whitaker test. Further discrepancies may be explained by intermittent obstruction which may be present at the time of one of the tests but not when the other is performed. In this regard it should be emphasised that both techniques are provocative and designed to demonstrate latent obstruction by accomplishing a high flow rate into the pelvicaliceal system. Thachil and Struthers (1983) have shown that the pressures within unobstructed upper urinary tracts in dogs are lower with a forced diuresis than with perfusion studies despite the achievement of similar flow rates during both tests. This is further evidence that the Whitaker test is a less physiological investigation than the diuresis renogram.

Previous reports have demonstrated a good correlation between the results of diuresis renography and renal pelvic morphology in adults (Lupton *et al.*, 1979) and in children (English *et al.*, 1982) with idiopathic hydronephrosis. If any investigation should be regarded as the "gold standard" in the assessment of these patients, renal pelvic morphological features have a strong claim because they are absolute indicators of the presence or absence of obstruction and are not subject to the potential inaccuracy of *in vivo* investigations. It is unfortunate therefore that there is, at present, no satisfactory method of obtaining pre-operative morphological information. Of interest is the fact that there is better agreement between the diuresis renogram and renal pelvic morphology than between the Whitaker test and the morphological features.

How does this study help the appraisal of hydronephrosis? Diuresis renography is a simple, safe and easily repeatable investigation which, in addition to assessing excretion of urine from the kidney, gives accurate information on relative function. There is an argument for using only this test for evaluating idiopathic hydronephrosis in that it can be performed serially and often enough to detect changes in function or excretion over a period of time. If the affected kidney functions poorly, diuresis renography is impractical and the Whitaker test should be used. It should also be used with a consistently equivocal diuresis renogram, especially after previous surgery. Non-obstructive diuresis renographic features in patients with troublesome loin pain may be a further indication, as may be obstructive renographic patterns in symptom-free patients with good preservation of renal function.

Both diuresis renography and the Whitaker test may be required in some cases of idiopathic hydronephrosis. We support the view of Koff (1984) that rather than asking which test is better, we should use both if necessary for the best possible description of anatomy, renal function and physiology to help make a logical decision on whether surgery is necessary.

Acknowledgements

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The Authors

E. W. Lupton, MD, FRCS, Consultant Urologist, University Hospital of South Manchester.

D. Richards, FRCR, Consultant Radiologist, University Hospital of South Manchester.

H. J. Testa, MD, PhD, MRCP, Consultant in Nuclear Medicine, Manchester Royal Infirmary.

S. A. Gilpin, Anatomy Research Technician, Manchester University.

J. A. Gosling, MB, MD, Professor of Anatomy, Manchester University.

R. J. Barnard, FRCS, Consultant Urologist, University Hospital of South Manchester.

Requests for reprints to: E. W. Lupton, Department of Urology, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR.

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Evaluation of Obstructive Uropathy in Children. ^{99m}Tc-DTPA Renography Studies under Conditions of Maximal Diuresis

R. N. SUKHAI[1], P. P. M. KOOY[2], E. D. WOLFF[3], R. J. SCHOLTMEIJER[4] and A. J. VAN DER HEIJDEN[1]

[1]*Department of Paediatrics Subdivision Nephrology, University Hospital, Rotterdam/Sophia Children's Hospital, Rotterdam;* [2]*Department of Nuclear Medicine, Erasmus University and University Hospital, Rotterdam; Departments of* [3]*Paediatrics and* [4]*Paediatric Urology, Erasmus University and University Hospital, Rotterdam/ Sophia Children's Hospital, Rotterdam, The Netherlands*

Summary—Renographic studies under standardised conditions of maximal diuresis provoked by hypotonic saline infusion and frusemide were used in 17 patients with dilatation of the upper urinary tract in order to distinguish between obstructed and non-obstructed urinary tracts. Of the six patients who were obstructed on clinical and X-ray evidence only three showed an obstructed pattern on the renographic curves after maximal diuresis. After operation these three patients showed improvement in both renographic curve and functional images of the renal parenchyma. A new method of identifying the parenchymal area is described.

Dilatation of the upper urinary tract is often seen in children. In most cases it is caused by obstruction, but in some the obstruction is only relative, as in the dilatation that accompanies increased urine flow in patients with the prune belly syndrome; occasionally there is no obstruction at all, as in megacalicosis (Johnston, 1973, 1977). Barratt and Chantler (1970) used the decreased fractional excretion of filtered water as an indicator for true obstruction. In another functional study (Bullock, 1983), the so-called "distal nephron index" was used as an indicator of distal nephron function in order to distinguish obstructed from non-obstructed urinary systems. He also carried out pressure-flow studies as described by Whitaker (1973). The Whitaker test has proved useful in many adult patients but is difficult to perform in children.

Britton *et al.* (1979) introduced the parenchymal transit time (PTT) of ^{99m}Tc-DTPA in adults with obstructive uropathy. This is obtained by deconvolution analysis and is prolonged in cases of obstruction.

Diuretic renography using ^{99m}Tc-DTPA has often been used to distinguish between obstructed and non-obstructed dilated systems (Koff *et al.*, 1980, 1982; Koff, 1982; Shore *et al.*, 1983). In all of these series the patients were studied first under normal hydrated conditions and then after intravenous administration of frusemide.

Since the aim of these tests is to detect those dilated urinary tracts in which the pressure or dilatation increases during increasing urine flow, we suggest that such studies should be performed under conditions of maximal diuresis. We have approached the problem by using ^{99m}Tc-DTPA renography under conditions of maximal diuresis provoked by hypotonic saline infusion and frusemide.

Patients and Methods

Thirteen boys and four girls (age range 2 months-14 years) were studied between June 1982 and

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Table 1 Details of Patients

Patients	*Age (years)*	*Sex*	*Pcreat (μmol/l)*	*Diagnosis*
1. J.Ve.	2/12	M	28	PUJ R
2. V.W.	1 9/12	M	46	PUJ R + reflux
3. M.B.	5 4/12	M	46	PUJ L
4. J.Vo.	3 1/12	M	30	PUJ R
5. H.V.	5 1/12	M	32	VUJ R
6. M.H.	5 11/12	F	42	VUJ L
7. R.R.	6	M	52 S	VUJ
8. S.Ph.	4 11/12	M	70 S	Anderson-Hynes plasty
9. J. de L.	14 8/12	M	84 S	dilated system
10. E. de V.	5 8/12	M	74	PUJ L
11. C.v.A.	5 3/12	F	45	PUJ L
12. J.B.	6 4/12	M	41	PUJ R
13. P.v.d.B.	2 3/12	M	34 S	PUJ L
14. E.v.N.	4 6/12	F	62	VUJ L
15. J.K.	8 8/12	M	54	PUJ R
16. P. de R.	8 2/12	M	57	VUJ L
17. J.v.d.T.	2 1/12	F	43 S	VUJ R

PUJ = Pelviureteric junction obstruction.
VUJ = vesicoureteric junction obstruction.
S = single kidney.
Pcreat = plasma creatinine.

March 1983. Age, sex, plasma creatinine level and diagnosis are shown in Table 1. All patients were in good clinical condition (except for patient no. 8, who had a solitary kidney) and all had normal plasma creatinine levels.

After an oral water load of 20 ml/kg body weight, hypotonic saline (NaCl 0.45% with glucose 2.5%) was administered intravenously over a 2-h period. The dose was 2000 ml/1.73 m^2 body surface.

Urine samples were collected during spontaneous voiding. Blood samples were taken from an indwelling venous catheter as described by Rodriquez-Soriano (1981).

After administration of the hypotonic saline solution, a ^{99m}Tc-DTPA scan was made using a gamma camera (LFOV, Siemens Gammasonics) and data collected in a computer (Gamma 11, DEC). The dose was 74 MBq/1.73 m^2, administered intravenously, with the patient supine. Computer data were collected in a 64 × 64 matrix, 54 frames of 20 s and 6 frames of 60 s. Gamma camera data were collected in 4 frames of 30 s. Two minutes after injection, 150,000 counts were collected and the collection time (T seconds) recorded. Starting at 5, 10, 15, 20 and 25 min after injection, data were again collected during a period of T seconds and the patient was then allowed to empty his bladder. Thirty minutes later 0.2 to 0.4 mg/kg body weight frusemide were given intravenously. Computer data were collected in the same way as before and gamma camera data collected for periods of T seconds at 5, 10 and 15 min after administration of the frusemide. Data analysis included visual inspection of the time-activity curves of regions around each kidney. In most cases the contralateral kidney functioned as a control for the time-activity curves. Curves from a normal kidney, an obstructed kidney and a dilated but not obstructed kidney are shown in Figures 1 and 2.

Our experience suggests that the renographic curve supplies sufficient information to determine whether or not there is obstruction. We attempted to quantify the degree of obstruction instead of relying solely on visual inspection. Initially we used the method described by Britton *et al.* (1979). In their study the data were used as they were collected during the whole scan period of 24 min. In our paediatric population it was not possible to distinguish the parenchymal area from the collecting system, a distinction which is essential in the method of Britton *et al.* Factors that caused difficulty were the over-projection of the collecting system during the last part of the scan and movements of the kidney during respiration, which caused the parenchyma to be overshadowed by the renal pelvis. We therefore tried to find a method which would use only a part of the scan period, particularly the first 7 min. During this period there is no significant overlap of the collecting system on the paren-

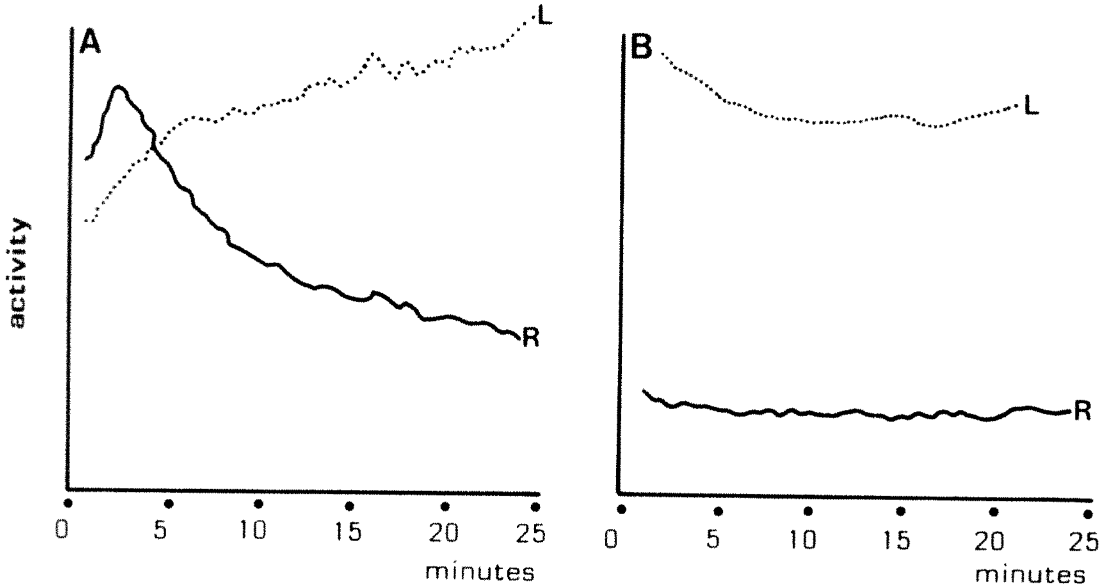

Fig. 1 (A) Left kidney (L) shows obstructive pattern, whereas right kidney (R) is normal after hypotonic volume expansion. (B) After frusemide the tracer activity in the right urinary system has already diminished, whereas accumulation of tracer activity remains in the left system, without drainage.

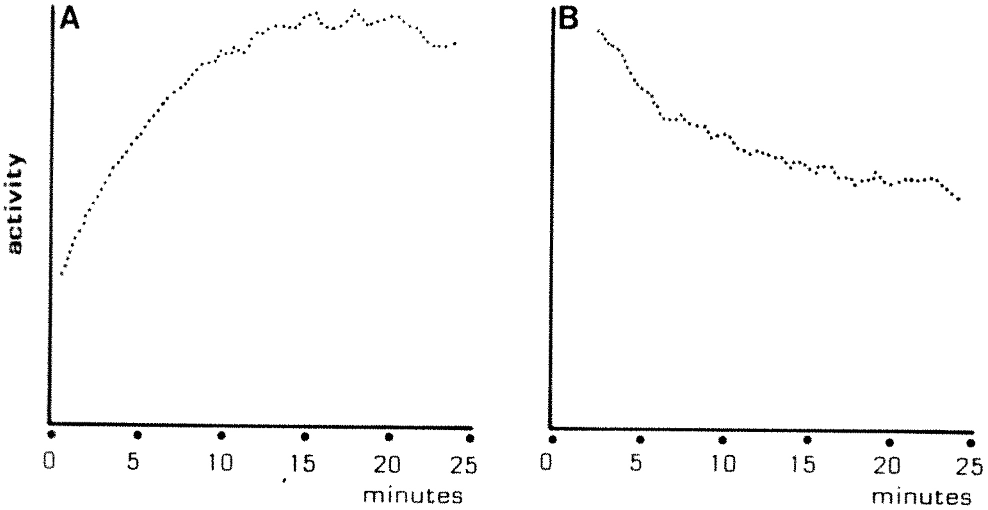

Fig. 2 (A) Under conditions of hypotonic volume expansion there is an accumulation of tracer counts in time. (B) After administration of frusemide the urinary system drains well in this patient with a single kidney.

chyma of the obstructed kidney and one can assume that for a normal kidney the kidney is visible, the maximal amount of tracer in the normal parenchyma has already been reached (about 2-4 min after injection of the isotope), and there is tracer activity in the collecting system of the kidney. The amount of such activity depends on the degree of obstruction.

From the data of every pixel obtained from the computer it is possible to construct two parameters which give an impression of kidney function. These are the maximal amount of tracer in a specific part of the kidney, and the time after injection of the isotope at which that maximal amount is reached (functional imaging). If kidney function is impaired, the amount of tracer will continue to increase in the first 7 min in both the parenchyma and the collecting system. It is then impossible, using

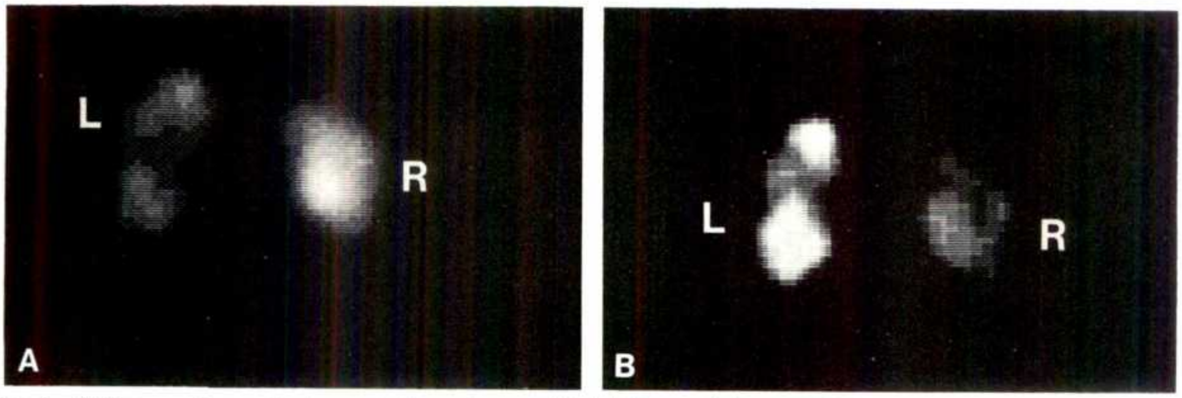

Fig. 3 (A) Pre-operative maximal amount of tracer in normal right kidney and obstructed left kidney (patient no. 11). The amount of tracer is less in the left parenchymal area and there is no activity in the left pelvis. In the right pelvis the concentration of tracer activity is normal. (B) Pre-operative corresponding time activity picture in patient no. 11. Normal right kidney with normal transit of tracer from parenchyma to pelvis and obstructed left kidney. The maximum amount of tracer in the left kidney is reached only at the end of the 7-min period.

the functional imaging technique, to distinguish between parenchyma and collecting system. To overcome this difficulty we added a limiting condition to the normal functional imaging. In a functioning kidney the amount of tracer must increase. We stipulate that it must increase by at least 5% per frame, if a given pixel is to be imaged. If the pixel does not satisfy the requirements for frame X and frame X + 1, we look at frame X + 2 and stipulate that the amount of tracer then has to have increased by at least a factor $(1.05)^2 = 1.1025$ in comparison with frame X, and so on. If, however, the amount of tracer in frame X + 1 meets the limiting condition, the amount of tracer in frame X + 1 is the new starting value.

We thus calculate the "maximal amount of tracer" only for those pixels which at some time during the scan fulfil the limiting condition. Our method has two advantages. (1) The influence of statistical variations, especially in the obstructed kidney, is reduced. (2) There is some improvement in contrast, and consequently in visibility, since those pixels that have a real increase in the amount of tracer are more likely to meet the limiting condition. This can be expressed as follows:

If a given pixel with a low amount of tracer is next to a pixel with a high amount of tracer, part of its tracer will be due to the adjacent pixel and "apparent" and part will be "real". If the high amount of tracer in the adjacent pixel increases by, say, a factor of 2, the apparent amount of tracer will also increase by a factor of 2, but if the "real" amount of tracer remains the same, the total amount of tracer increases by less than a factor of 2. Only if the "real" amount of tracer increases by a factor of 2 or more can the total amount of tracer increase by a factor of 2. In our patients the limiting condition of an increase of 5% has produced good resolution.

The results of our calculations are presented in Figure 3. The maximal amount of tracer and the corresponding frame number are visualised on a grey scale, white representing the highest value. Figure 3 shows a patient with pelviureteric junction obstruction on the left. In Figure 3B the right kidney shows a normal activity picture with a low frame number in the parenchyma and a high frame number in the collecting system. The left kidney shows a pattern corresponding to obstruction, with a low frame number in the collecting system and a high frame number in the parenchyma. Figure 3A shows the corresponding maximal amount of tracer. After relief of the obstruction (Fig. 4) we see a normal pattern of distribution in the left kidney which has also become smaller. With this modified functional imaging method one can deduce from the combination of the maximal amount of tracer and the corresponding frame number which parts of the kidney are draining well and which are not. In addition, it is possible to detect recovery in the kidney after operative relief of obstruction.

Results

The accumulated data are shown in Table 2. Of the 17 patients examined, 11 did not have urinary obstruction and 6 had urinary obstruction on clinical and X-ray evidence. After volume expansion with hypotonic saline 10 of the 11 patients in the non-obstructed group were confirmed as non-

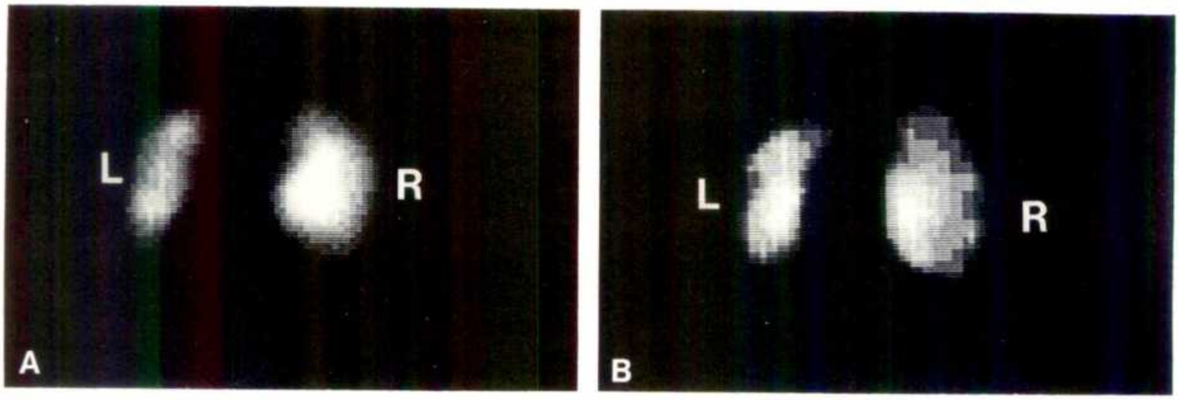

Fig. 4 (A) Post-operative maximal amount of tracer (patient no. 11). Normal right kidney and unobstructed pattern in left kidney. The left kidney has become smaller post-operatively and maximal tracer activity is present over the whole kidney. (B) Corresponding post-operative time activity picture in patient no. 11, showing unobstructed pattern on the left. Maximal activity is reached before the end of the 7-min period.

Table 2 Results after Intravenous Urography, Hypotonic Volume Expansion and Hypotonic Volume Expansion plus Frusemide

	After				
Patients	*IVP+ clinical examination*		*HVE*		*HVE+ frusemide*
NO	11	10 →	12	12 →	14
		1 ↘ 2 ↗		2 ↗	
O	6	4 →	5	3 →	3
Total	17				

NO = not obstructed.
O = obstructed.
HVE = hypotonic volume expansion.

obstructed. The remaining patient showed equivocal obstruction on the intravenous urogram, a relatively obstructed urine flow after volume expansion, but a non-obstructive pattern after administration of frusemide.

After volume expansion, only four of the six patients originally judged to be obstructed had an obstructed urine flow. After frusemide, only three of the six patients continued to show an obstructive pattern.

In the three patients with confirmed urinary obstruction after volume expansion and frusemide (cases 10, 11 and 12 in Table 1), a percutaneous nephrostomy was placed under sonographic control. Six weeks later an Anderson-Hynes pyeloplasty was performed to relieve the pelviureteric junction stenosis. Histological investigation of the ureter near the pelviureteric junction showed increased collagenous fibres in one patient, an abnormal arrangement of muscle fibres in another, and no marked abnormalities in the third patient. In these three patients, a ^{99m}Tc-DTPA renal scan was performed before and after nephrostomy and 3 to 6 months after pyeloplasty. All showed improved renographic curves after nephrostomy drainage and this improvement was also apparent after pyeloplasty. Also, the functional parenchymal areas estimated from the "time-activity" curve increased after nephrostomy drainage and pyeloplasty, indicating functional recovery of the affected kidney (Fig. 4). The three patients who had been judged obstructed on clinical and X-ray evidence, but who were shown not to be obstructed by hypotonic volume expansion and administration of frusemide, have been followed up for periods of 3 to 6 months. In each case a second hypotonic volume expansion study again proved normal. In one patient a Whitaker pressure-flow study was performed and this also gave a normal result.

Discussion

To judge whether obstruction is present or not is still a problem in children with dilatation of the upper urinary tract. Renographic studies with diuretics (Koff *et al.*, 1980, 1982; Shore *et al.*, 1983) are helpful, but are performed under conditions of normal hydration, and because obstruction is defined as increased pressure under conditions of increased urine flow (Walker *et al.*, 1980), these patients should be investigated under conditions of maximal diuresis. From practical experience we know that most patients complain when they are given a large oral fluid intake. Oral loading followed by intravenous hypotonic volume expansion was sufficient to show that two patients originally judged on clinical and X-ray grounds to be obstructed were in fact not obstructed. With the addition of frusemide one further patient in the same group (case no. 9, Table 1) was found to have no functional obstruction. This patient had an obstructive pattern during hypotonic volume expansion with a constant urine flow rate. When frusemide was administered it promoted an increase in urine outflow from the dilated pelvic system and therefore, after the extra filling of the urinary system with frusemide, the system drained well; this patient had massive dilatation of kidney and ureter. We believe that maximal filling of the urinary system is of critical importance in preventing false positive diuretic renograms. Shore *et al.* (1983) described a patient with an obstructive pattern on renographic studies under conditions of normal hydration even though he had had a successful operation for PUJ obstruction and a Whitaker test was normal. It is possible that maximal diuresis provoked by hypotonic volume expansion and frusemide might have shown a non-obstructive pattern. Thus we believe that a diuretic renographic study as described by Koff *et al.* (1980, 1982) and Shore *et al.* (1983) is discriminatory only in marginally dilated urinary systems and not in the massively dilated systems that are often observed. As already mentioned, the studies in adults proposed by Britton *et al.* (1979) could not be used successfully in children.

Functional imaging of the parenchyma, as described here, yielded information on recovery of the individual kidney before the obstruction had been relieved. Further studies in this field are required.

It is concluded that renographic studies in which maximal diuresis is provoked by hypotonic volume expansion provide the best method of judging whether or not there is obstructive uropathy. In the follow-up of patients with obstruction it is very important to perform these studies under standard conditions. The so-called frusemide washout may not be necessary in all patients but is valuable in those with massive dilatation of the urinary system. It is hoped that the detection and imaging of functional parenchymal areas and collecting systems will lead to a better understanding of the nature of obstruction.

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We thank Professor T. M. Barratt, Dr I. Gordon and Dr G. Vivian, Hospital for Sick Children, London, for lively discussions in the early phase of this study. We also thank Dr A Piepsz, St Peters Ziekenhuis, Free University of Brussels, for his advice. Finally, we thank Miss E. Berkouwer for typing the manuscript.

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The Authors

R. N. Sukhai, MD, Paediatric Nephrologist.
P. P. M. Kooy, PhD, Research Fellow, Department of Nuclear Medicine.
E. D. Wolff, MD, PhD, Head of Paediatric Nephrology.
R. J. Scholtmeijer, MD, PhD, Professor of Paediatric Urology.
A. J. van der Heijden, MD, Paediatric Nephrologist.

Requests for reprints to: R. N. Sukhai, Department of Paediatrics, Subdivision Nephrology, Sophia Children's Hospital, Gordelweg 1600, 3038 GE Rotterdam, The Netherlands.

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Management of Patients with Renal and Ureteric Calculi Presenting with Chronic Renal Insufficiency

N. P. GUPTA, G. S. KOCHAR, S. N. WADHWA and S. M. SINGH

Department of Urology, All-India Institute of Medical Sciences, New Delhi, India

Summary—Of 403 patients with renal and ureteric calculi treated during the last 4 years, 64 presented with features of chronic renal insufficiency: 59 of these underwent surgery. Good pre-operative preparation and conservative renal surgery restored normal renal function in 14 patients and 27 improved significantly. The remainder either did not improve or continued to have progressive renal failure. It is emphasised that these patients are considerably worse off compared with their counterparts with normal renal function. The overall mortality rate was 17%. Patients whose post-operative serum creatinine levels did not stabilise to less than 884 μmol/l seemed to make poor progress in the follow-up period.

Asymptomatic and neglected urinary calculi are the second commonest cause of chronic renal failure in patients seen at this Institute and they form 10 to 15% of the total number of cases. Responsibility for the neglect may lie with the patient himself or with his physician in not prescribing orthodox treatment (Singh *et al.*, 1980). Calculi may cause renal damage by obstruction and infection, by associated interstitial cystitis and hypertension or by damage to the renal parenchyma during surgery for stone removal. Renal insufficiency leads to higher operative morbidity and mortality. Singh *et al.* (1973) emphasised the dangers of the unoperated staghorn calculus and recommended surgery even for asymptomatic stones. Mebel *et al.* (1982) also demonstrated the superiority of the surgical approach over conservative treatment in patients with nephrolithiasis and chronic renal failure. Recovery of the renal parenchyma is often remarkable and in most of these patients dialysis or renal transplantation can thus be avoided (Singh *et al.*, 1982).

Patients and Methods

A retrospective analysis of 403 patients with upper urinary tract calculi admitted to our Urology Service between January 1980 and December 1983 revealed that 64 had varying degrees of renal insufficiency, with blood urea levels >6.6 mmol/l and serum creatinine levels > 177 μmol/l. This high incidence of renal impairment is attributed to the complicated nature of the cases handled by this referral unit. Patients presenting with calculus anuria have been excluded from the study.

The patients ranged in age from 10 to 70 years and the male to female ratio was 8 : 1 (Fig.). Analysis of their symptoms revealed that 20% had suffered no pain; five gave a history of painless haematuria and six presented only with gastrointestinal symptoms which were due to chronic renal failure (Table 1). The duration of symptoms ranged

Table 1 Principal Symptoms in 64 Patients

Symptom	*No. of patients*	%
Pain	51	80
Urinary tract infection	44	70
Gastrointestinal	43	67
Haematuria	31	48

NB Thirteen patients had no pain, 6 had gastrointestinal symptoms only and 5 had painless haematuria.

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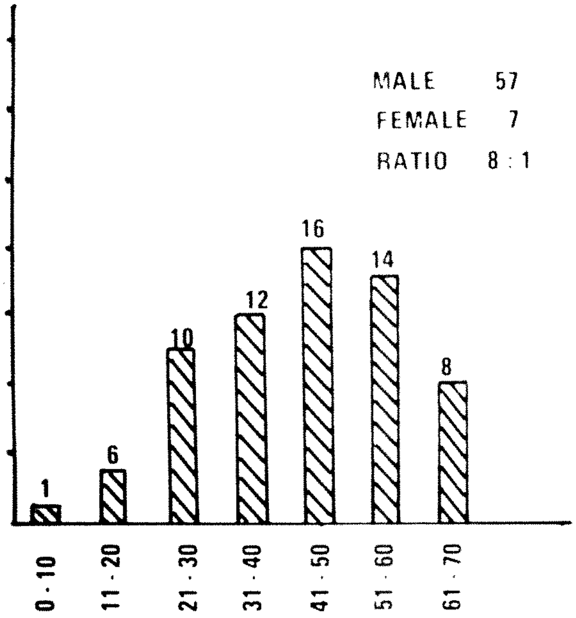

Fig. Age and sex incidence in 64 patients.

from 2 weeks to 21 years and did not correlate with the presence or absence of renal insufficiency. Over half of the patients were known to have calculus disease and one-third were known to be hypertensive; 18 patients had undergone surgery in the past for urolithiasis and four had undergone nephrectomy for complications arising from calculus disease. The commonest physical findings were pallor, hypertension and oedema (Table 2).

Table 2 Physical Findings in 64 Patients

	No. of patients	%
Pallor	59	92
BP >160/90	32	50
Oedema	22	40
Renal mass	18	28
Cardiac failure	6	9
Pericarditis	2	3

Pre-operative blood urea ranged from 7.33 to 56.66 mmol/l and the corresponding serum creatinine ranged from 221 to 1592 μmol/l (Table 3). Creatinine clearance ranged from 1 to 44 ml/min (mean 9.5). Hypercalcaemia was found in one patient, hypercalciuria in three and hyperuricosuria in three. Forty-one patients (64%) had hyperuricaemia, probably related to the impaired renal function. High dose intravenous urography, using 2 ml/kg body weight of 76% Urografin, was performed in 54 patients; it showed non-visualisation of one kidney in 25 patients and gave no worthwhile information in 8 cases. Ultrasonography was performed in eight patients and isotope renal scan in nine. More recently we have preferred the combination of ultrasonography and renal scan to high dose urography. Retrograde pyelography to delineate the obstruction further was performed in 22 patients. The location of the stones was unilateral ureteric in 5 patients, bilateral ureteric in 11, unilateral renal in 14, bilateral renal in 16, unilateral renal + ureteric in 5 and bilateral renal + ureteric in 13.

Table 3 Pre-operative Investigations

Blood Urea (mmol/l)	*No. of patients*	*Serum Creatinine (μmol/l)*	*No. of patients*
6.66-16.66	27	221-442	23
16.67-33.33	20	443-884	19
33.34-34.50	9	885-1320	11
>50	8	>1320	11
Total	64		64

Dialysis was used in 30 patients. In some it was a prophylactic measure aimed at improving the patient's clinical and biochemical status prior to surgery. Fifty-three dialysis sessions were given to these 30 patients. Post-operative dialysis was required in nine patients. In all but three instances, haemodialysis was given because of its greater efficiency.

Fifty-nine of the 64 patients were operated upon. Of the remaining five, three were considered unfit for any form of anaesthesia, one refused surgery and one was found to have bilateral uric acid stones which dissolved with medical management alone. Sixty-eight operative procedures (1–4 per patient) were performed on these 59 patients. The commonest procedures were ureterolithotomy (25), pyelolithotomy (20) and nephrostomy (19). Nephrolithotomy was performed in 7 cases, pyelonephrolithotomy in 6, uretero-pyelolithotomy in 4 and Evans' loop/basketing in 2. An attempt was made to avoid incisions on the renal parenchyma and, where necessary, these took the form of small radial nephrotomies. In all instances of bilateral renal stones, the better functioning kidney was operated upon first.

Results

Post-operative blood urea ranged from 3.5 to 53.3 mmol/l and was restored to normal in 14 patients. It was significantly improved in another 26 patients and remained unchanged in eight. The remaining 11 patients continued to have progressive renal failure despite removal of their calculi. Post-operative serum creatinine ranged from 106.06 to 1478 µmol/l (mean 424 µmol/l). Overall, 40 of 59 patients were improved by surgery, 8 were unchanged and the rest continued to have progressive renal failure.

Of the 8 patients who did not improve significantly, 2 died, 4 are alive and 2 are lost to follow-up. Of the 11 patients who continued to deteriorate, only 1 is alive, 6 have died and 4 are lost to follow-up. Six patients died in the post-operative period and another 5 during follow-up (range 6 months–4 years), giving an overall mortality rate of 17%. This includes three deaths in the group of unoperated patients. It is likely that some of those lost to follow-up have also died, giving an even higher mortality figure.

Apart from the high mortality rate, these patients also suffered considerable morbidity. Complications were noted in 22 patients (37%) (Table 4). The mean post-operative hospital stay for these patients was 28 days. Blood pressure came down to normal in 15 patients, was better controlled in 7 and remained unchanged in 10.

Discussion

Renal calculus disease forms an important and preventable cause of renal failure in many countries. Not only stones and their pathological consequences but also surgery to remove them, at least in some instances, contribute to the ultimate loss of functioning nephrons. Our experience of conservative renal operations in 59 of 64 patients known to have chronic renal insufficiency indicates that these patients are far worse off, in terms of morbidity and post-operative and long-term mortality, than their counterparts with normal renal function. For patients with calculus disease without renal failure, the mortality rate was less than 1%, the complication rate less than 5% and the mean post-operative hospital stay less than 10 days. Once renal insufficiency was established, the mortality rate in this series was 17%, the complication rate 37% and the mean post-operative hospital stay 28 days. On the brighter side is the fact that two-thirds of these patients derived significant and lasting benefit from surgery; they were freed from pain, haematuria and infection, and several were saved from chronic haemodialysis. Notable factors amongst those who did not improve were a persistently high blood urea and creatinine level in the post-operative period and a long previous history of deteriorating renal failure.

Table 4 Complications in 22 Patients

Wound infection	13
Residual calculus	9
Urinary tract infection	6
Secondary haemorrhage	5

We continue to see and treat many patients with silent or neglected urinary calculi who have slipped into varying degrees of renal insufficiency. Although many would appear initially to have a hopeless prognosis, it should be possible, with the help of detailed pre-operative assessments, correction of underlying biochemical abnormalities, appropriate radiological investigations and the use of dialysis, to help many of these patients and give them a reasonably good quality of life.

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The Authors

N. P. Gupta, MS, MCh(Urol), Assistant Professor.
G. S. Kochar, MS, MCh(Urol), Senior Resident.
S. N. Wadhwa, MS, MCh(Urol), Associate Professor.
S. M. Singh, FRCS, FAMS, Professor and Head of Department of Urology.

Requests for reprints to: N. P. Gupta, Department of Urology, All-India Institute of Medical Sciences, New Delhi-110029, India.

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Thallium-Technetium Subtraction Scintigraphy as an Aid to Parathyroid Surgery

R. C. PERCIVAL, G. M. BLAKE, G. H. URWIN, J. L. WILLIAMS and J. A. KANIS

University Department of Human Metabolism and Clinical Biochemistry; Departments of Medical Physics and Urology, Royal Hallamshire Hospital, Sheffield

Summary—We describe the application of thallium-technetium subtraction scintigraphy in nine patients with failed previous parathyroid surgery or with tertiary hyperparathyroidism due to chronic renal failure. The technique successfully located all adenomas, but only 45% of hyperplastic glands. The series included three abnormal glands located retrosternally. The technique appeared to be more useful in patients with primary hyperparathyroidism than in tertiary hyperparathyroidism, possibly related to differences in gland mass. We conclude that this method of scintigraphy is a valuable adjunct to the management of patients with parathyroid disorders, particularly those requiring revision surgery.

The prognosis following surgical treatment of primary hyperparathyroidism is extremely good, and associated with a very low incidence of morbidity (Brennan *et al.*, 1982). Problems arise most commonly in patients who have had prior neck exploration, or in patients with uraemia in whom prolonged surgery is best avoided. In such situations, the use of reliable techniques to localise parathyroid tissue before surgery would be advantageous.

A number of techniques, both invasive and non-invasive, have been evaluated. These include selective venous catheterisation and selective arteriography, as well as attempts to image parathyroid tissue with ^{75}Se selenomethionine or ^{131}Cs caesium chloride. The method most widely used is selective venous sampling, and the subsequent assay of parathyroid hormone which accurately localises parathyroid tissue in up to 60% of patients (Brennan *et al.*, 1982). The limitations of this technique include the morbidity associated with the procedure and the expertise required. Further problems arise in chronic renal failure where the delayed metabolic clearance of inert fragments of parathyroid hormone in the circulation poses difficulties with some of the radioimmunoassays commonly available. The greatest difficulties arise in patients who have undergone previous parathyroid surgery, in whom dissection and subsequent fibrosis may distort the vascular anatomy.

Ferlin *et al.* (1983), Young *et al.* (1983) and Percival *et al.* (1985) have reported that the technique of thallium-technetium scintigraphy successfully locates the vast majority of parathyroid adenomas. However, in order to confer significant advantages over other techniques available, it is important to determine its value in patients who have previously undergone neck surgery, or patients with tertiary hyperparathyroidism due to chronic uraemia.

Patients and Methods

For the past 18 months we have studied all patients at the Royal Hallamshire Hospital referred for parathyroidectomy. The diagnosis of hyperparathyroidism was made either on the basis of inappropriately increased serum concentrations of parathyroid hormone in the presence of hypercalcaemia, or, in the case of patients with end-stage

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Table Details of patients

Patient number	*Number of glands viewed by scan*	*Operative findings*		*Previous surgery*	*Diagnosis and additional details*
		Histology	*Gland size (g)*		
1	1	Adenoma	3.5	Partial thyroidectomy	Primary hyperparathyroidism
2	1	Hyperplasia	1.2, 0.4	3 previous explorations	Multiple endocrine adenomatosis with 1 retrosternal gland
3	1	Adenoma	6.3	Partial thyroidectomy	Primary hyperparathyroidism
4	1	Unknown	—	Failed parathyroidectomy	Primary hyperparathyroidism, thyroid nodule excised
5	1	Adenoma	5.4	Failed parathyroidectomy	Primary hyperparathyroidism, 1 retrosternal gland
6	0	Hyperplasia	7.3, 3.1, 0.4, 0.4	—	CRF
7	2	Hyperplasia	3.3, 2.1, 0.6	—	CRF
8	1	Adenoma	19.0	—	CRF, retrosternal gland
9	2	Hyperplasia	1.7, 1.25	—	CRF

Patients 6-9 had tertiary hyperparathyroidism associated with chronic renal failure (CRF), and the remaining patients primary hyperparathyroidism. For each patient the columns indicate the number of glands viewed on scintigraphy, the pathological findings and the number of abnormal glands excised.

renal failure, by radiography and the presence of hypercalcaemia. In order to avoid bias in the diagnostic accuracy of the scintigraphic technique, the decision to undertake parathyroid surgery was taken before performing the scan, and the outcome of the scan did not affect that decision. Over this period a total of 40 patients undergoing parathyroidectomy have been examined by thallium-technetium subtraction scintigraphy. This report concerns 9 patients, 5 of whom had had previous neck exploration, and 4 with tertiary hyperparathyroidism due to chronic renal failure.

The details of the scintigraphic technique have been described previously (Percival *et al.*, 1985). The principle of the method depends on the uptake of thallium by both parathyroid and thyroid tissue (Fig. 1), and the selective uptake of technetium by the thyroid gland (Fig. 2). By means of a Nova 4 minicomputer, the technetium thyroid image is then subtracted from the thallium image using different trial factors until optimum subtraction of the thyroid is achieved. Enlarged parathyroid glands are visible as focal areas of excess thallium activity superimposed on a background of uniform emission (Fig. 3). All scintiscans were interpreted by one observer (GMB) and a written report recorded before surgery.

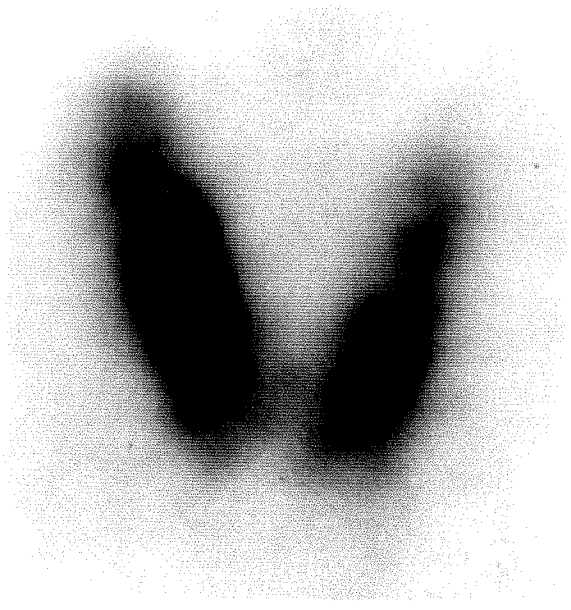

Fig. 1 ^{201}Tl thallous chloride is taken up by both parathyroid and thyroid tissue.

Results

Details of the scintigraphic, pathological and surgical findings in the nine patients are summarised in Table 1. In patients with previously failed parathyroid surgery all three adenomas were successfully located before surgery, including one patient in whom a retrosternal adenoma was positively identified (Fig. 4). A further patient (number 2, Table 1) had two hyperplastic glands, the larger of which was visible on scintigraphy but in a retrosternal position before surgery. In this patient,

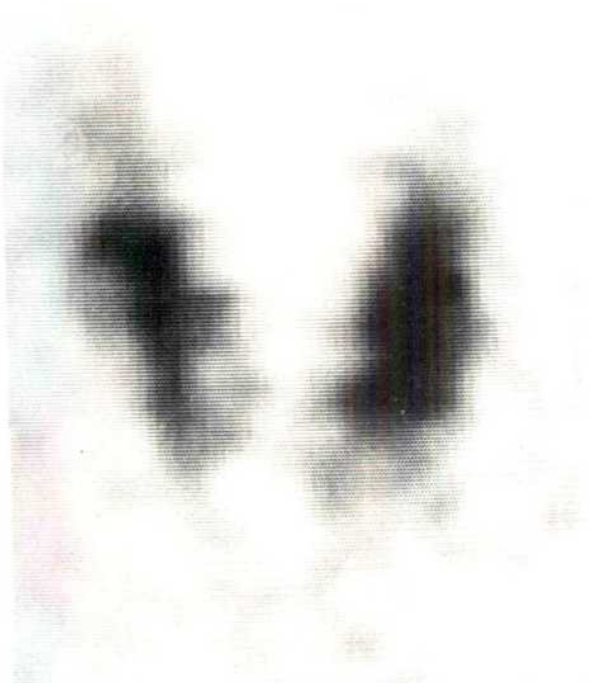

Fig. 2 ^{99m}Tc sodium pertechnetate is taken up only by thyroid tissue.

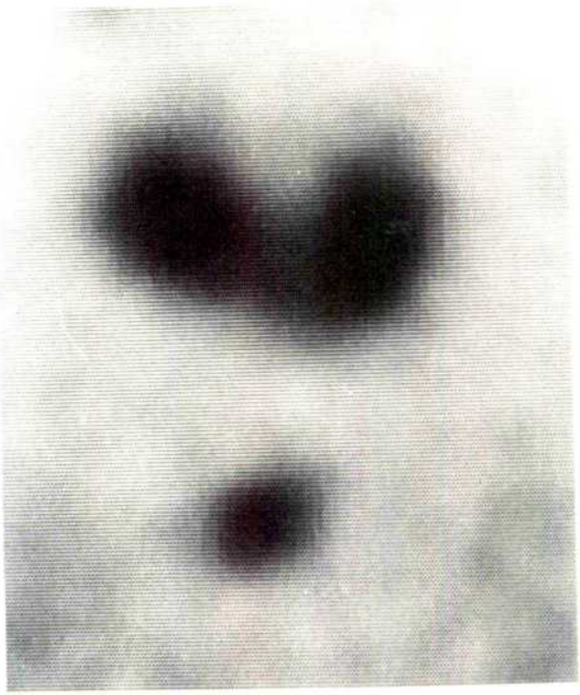

Fig. 4 Thallium image demonstrating a retrosternal parathyroid gland. A 5.4 g adenoma was excised at surgery.

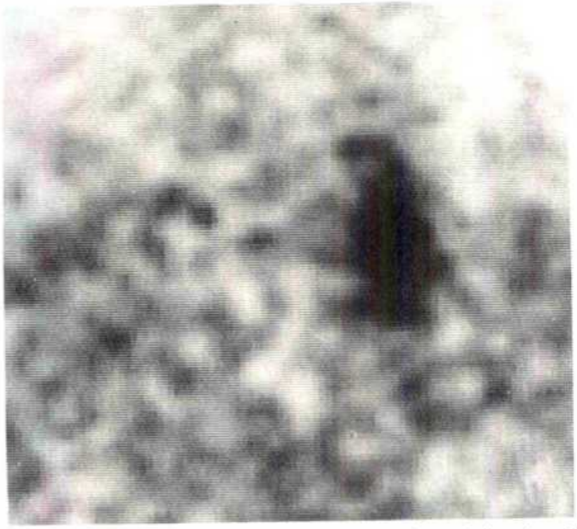

Fig. 3 The image obtained after subtraction of the thyroid technetium image from the thallium image. It shows a left upper pole adenoma which weighed 1.1 g at surgery.

previous selective venous catheterisation and subsequent measurements of parathyroid hormone were unhelpful in determining its location preoperatively. In one patient (number 4) an area of increased uptake was visible, which was subsequently found to be a thyroid nodule (Fig. 5). No parathyroid tissue was excised and this was the only false positive result encountered in our series of 40 patients.

The ability of subtraction scintigraphy to detect abnormal glands was less in the case of uraemia than in primary hyperparathyroidism (50 *v* 80%). However, this series included one patient with an adenoma in whom the gland was readily visible on scintigraphy, and lay in the retrosternal space. In a further patient (number 6, Table 1) two large hyperplastic glands were missed. However, this was the first thallium subtraction scan performed, and there were several technical difficulties in its interpretation. Thus the procedure successfully detected all parathyroid adenomas but only 45% of hyperplastic glands, so that the technique correctly identified 67% of all abnormal parathyroid tissue. The disparity between the ability of the technique to locate hyperplastic or adenomatous glands may relate to the differences in parathyroid gland mass. The weights of adenomas ranged between 3.5 and 19 g, whereas the weight of hyperplastic glands was less than 1 g in 50%.

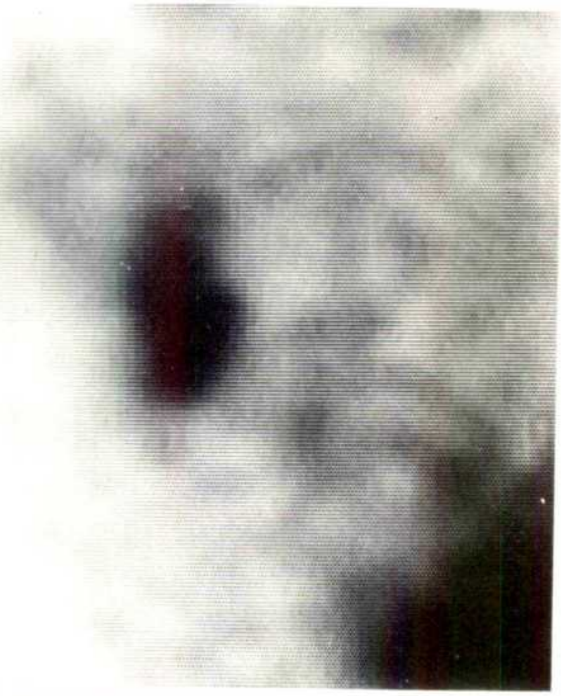

Fig. 5 Subtraction scan showing thallium uptake in a thyroid nodule—erroneously thought to be a parathyroid adenoma.

Discussion

The results of this study suggest that thallium technetium subtraction scanning is of particular value in delineating parathyroid adenomas in patients undergoing revision parathyroid surgery, including patients in whom abnormal parathyroid glands are located in a retrosternal position. The technique, as noted by Young *et al.* (1983), is less useful in detecting parathyroid hyperplasia which may be related in part to the smaller gland mass of hyperplastic tissue and the inability of the technique to define two glands in close anatomical proximity. A further limitation of the technique is the presence of a thyroid goitre, detectable on the technetium scan, which renders the subtraction procedure undiagnostic.

Because the procedure is non-invasive and accurately locates the vast majority of parathyroid adenomas (Ferlin *et al.*, 1983; Young *et al.*, 1983), it has clear advantages over selective venous catheterisation, particularly in patients who have had previous neck surgery. The high degree of success compares favourably with high resolution ultrasonography (Reading *et al.*, 1983), but major difficulties arise with this technique in locating gland in the retrosternal or retroclavicular region. Th role of parathyroid scanning in tertiary hyperparathyroidism requires further evaluation, but th disappointing results suggest that a false negativ scan should not be deemed a contraindication t surgery.

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The Authors

R. C. Percival, FRCS, Wellcome Surgical Research Fellow.
G. M. Blake, MA, PhD, formerly Senior Physicist, Department of Medical Physics. Now Senior Physicist, Wessex Regional Medical Physics Department, Southampton General Hospital.
G. H. Urwin, FRCS, Wellcome Surgical Research Fellow.
J. L. Williams, FRCS, Consultant Urologist.
J. A. Kanis, FRCP, MRCPath, Reader in Human Metabolism and Clinical Biochemistry.

Requests for reprints to: J. A. Kanis, Department of Human Metabolism and Clinical Biochemistry, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX.

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Use of a Ureteric Nipple in the Surgical Management of Bilharzial Ureteric Strictures

B. ELEM

Urology Unit, Department of Surgery, University Teaching Hospital, Lusaka, Zambia

Summary—Experience in the use of a ureteric nipple in ten patients with bilharzial strictures of 15 ureters is presented. It is recommended that this method should be the procedure of choice in the surgical management of selected cases of bilharzial ureteropathy. The need for further experience in its use in calcified ureters is stressed.

Obstructive uropathy is a serious and not infrequent complication of *Schistosoma haematobium* infestation of the urinary tract. Contrary to previous observations, it seems that distal ureteric stenosis is by far the most common cause of obstruction in this parasitic disorder (Smith *et al*., 1977). In the absence of severe structural damage to the affected ureters, such patients are usually managed by vesicoureteric reimplantation, but the gross dilatation of the ureters and the intense periureteritis make it difficult and dangerous to use an anti-refluxing type of reimplantation by submucosal tunnelling. Fam (1964) introduced a simple end-to-side ureterovesical anastomosis which has been widely employed in bilharzial surgery (Ghoneim *et al*., 1971; Mee and Youssef, 1982).

Urquhart-Hay *et al.* (1977) have recently reported the anti-reflux potential of vesicoureteric reimplantation by constructing a nipple from a dilated ureter without submucosal tunnelling. This is a simple technique but there is no previous report of its use in the management of dilated ureters, bilharzial or otherwise.

Patients and Methods

Ten males (average age 31 years), with bilharzial strictures of 15 ureters, have been managed by this

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Table Salient Features of the 10 Patients

No.	*Patient and age (years)*	*Radiological calcification*	*Ureters involved*	*Post-operative IVU*	*Post-operative MCUG*	*Follow-up*
1	G.T. (19)	Vesical	Bilateral	Marked improvement	None	3 years +
2	F.T. (36)	None	Left	Marked improvement	None	3 years +
3	P.P. (31)	None	Right	Marked improvement	None	3 years +
4	A.B. (30)	Vesical and ureteric	Right	Marked improvement	None	3 years
5	R.P. (29)	Vesical	Bilateral	Marked improvement	None	2 years +
6	F.M. (40)	Vesical and ureteric	Bilateral	No improvement	Bilateral reflux at rest	2 years +
7	E.M.V. (35)	None	Bilateral	Marked improvement	No reflux	2 years +
8	E.P. (39)	None	Bilateral	Marked improvement	No reflux	20 months
9	E.M. (30)	None	Left	Marked improvement	No reflux	16 months
10	G.E. (17)	None	Right	Marked improvement	No reflux	14 months

method (Table). All underwent pre-operative cystoscopy, micturating cystography (MCUG), intravenous urography (IVU) and fluoroscopy of the ureters. During cystoscopy under general anaesthesia, the bladder capacity was measured, a bladder biopsy obtained and the appearance of the ureteric orifices was noted. Any ureter failing to exhibit peristalsis during fluoroscopy for 60 s was considered atonic. A patient with atonic ureters, vesicoureteric reflux or a reduced bladder capacity (<300 ml) was considered unsuitable for nipple reimplantation. MCUG and IVU were repeated on all patients 6 months after operation and subsequently an IVU was carried out annually.

Findings

All ten patients had symptoms, mainly loin pain. There was no biochemical evidence of impaired overall renal function. The orifices of all 15 ureters appeared stenosed at cystoscopy and the IVU provided evidence of stenosis of the supravesical ureteric segments in all but two cases. All ureters also depicted a varying degree of dilatation and tortuo-

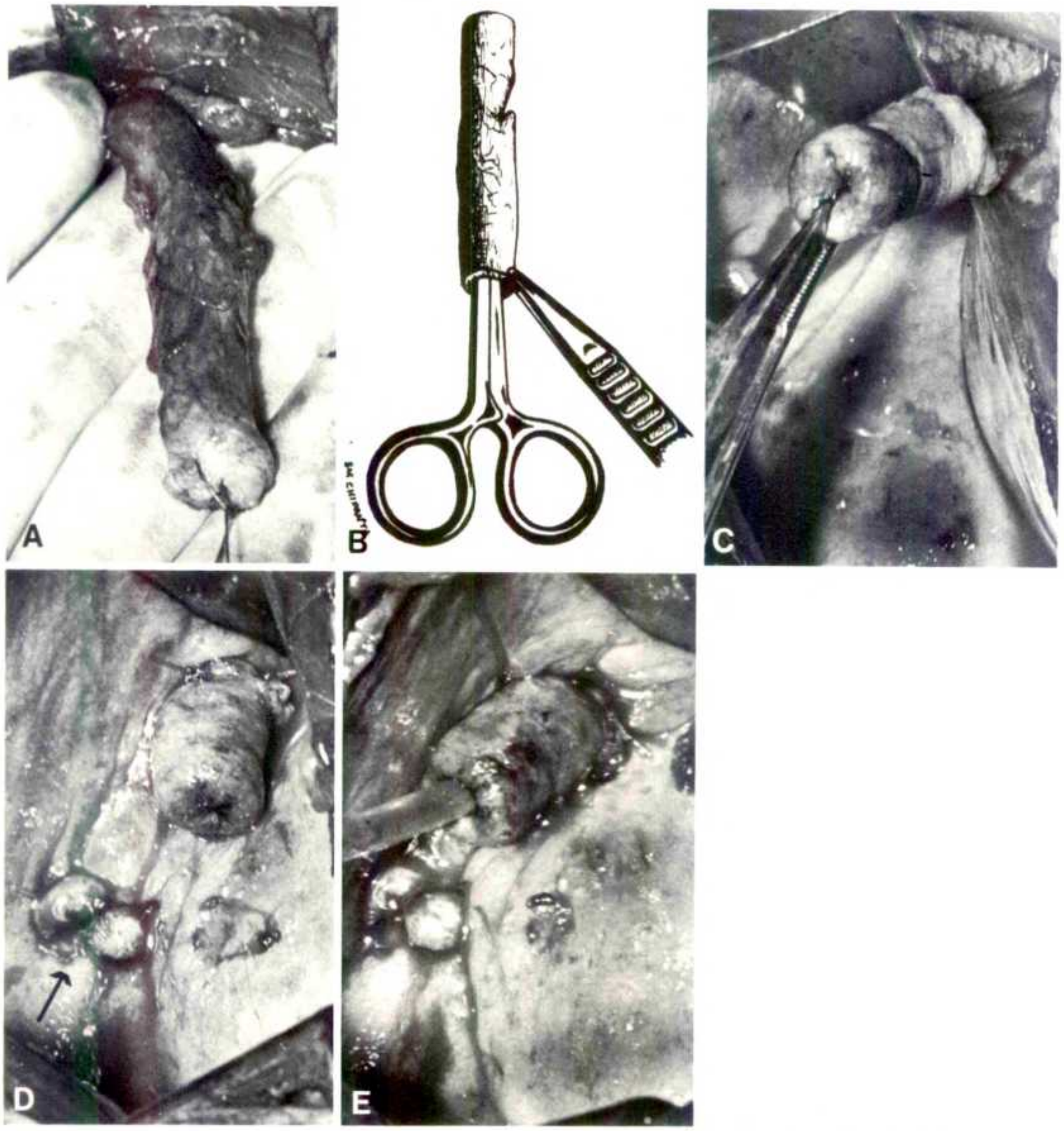

Fig. 1 (A) Grossly dilated ureter dissected free and lying outside the bladder. (B) A haemostat grasping the mucosa of the ureteric lumen. (C) The ureter being rolled back to form a nipple. (D) The nipple anchored to the bladder wall. Arrow pointing to the original site of the ureteric orifice. (E) The splinted nipple.

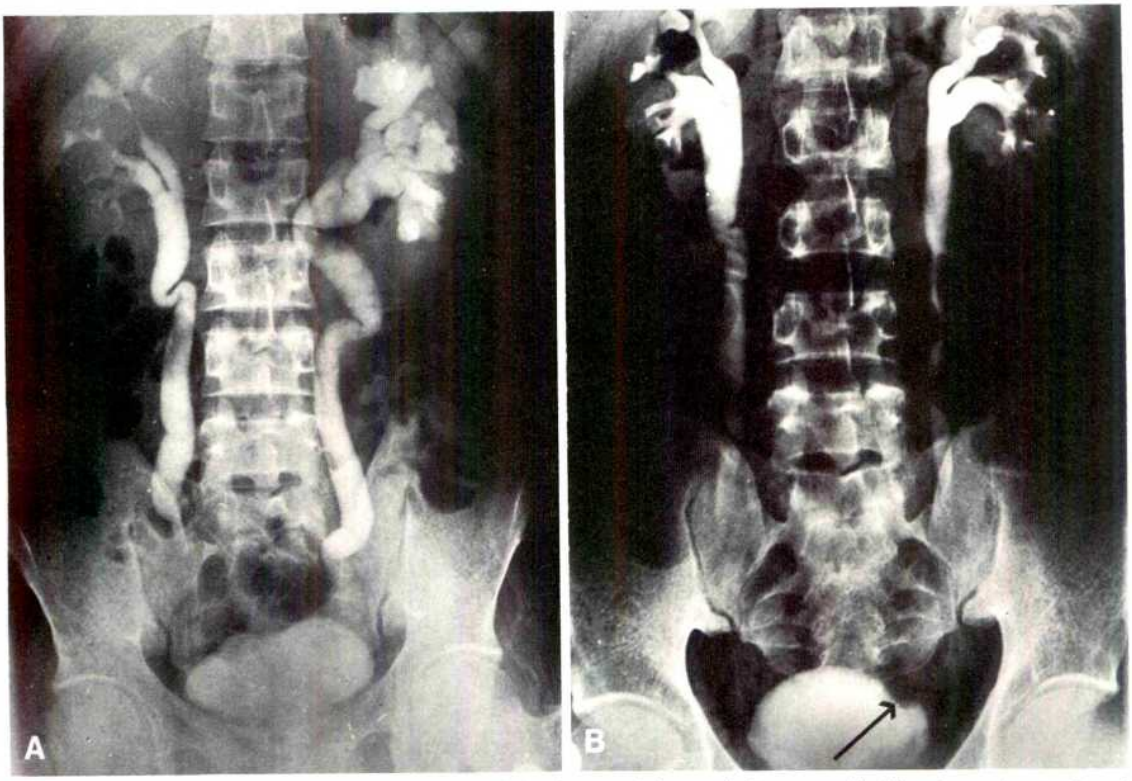

Fig. 2 (A) Pre-operative IVU of Case 7. Bilateral bilharzial strictures of the terminal ureters with dilatation and tortuosity of the proximal segments and left hydronephrosis. (B) IVU 2 years after surgery. Arrow indicates filling defect produced by the nipple.

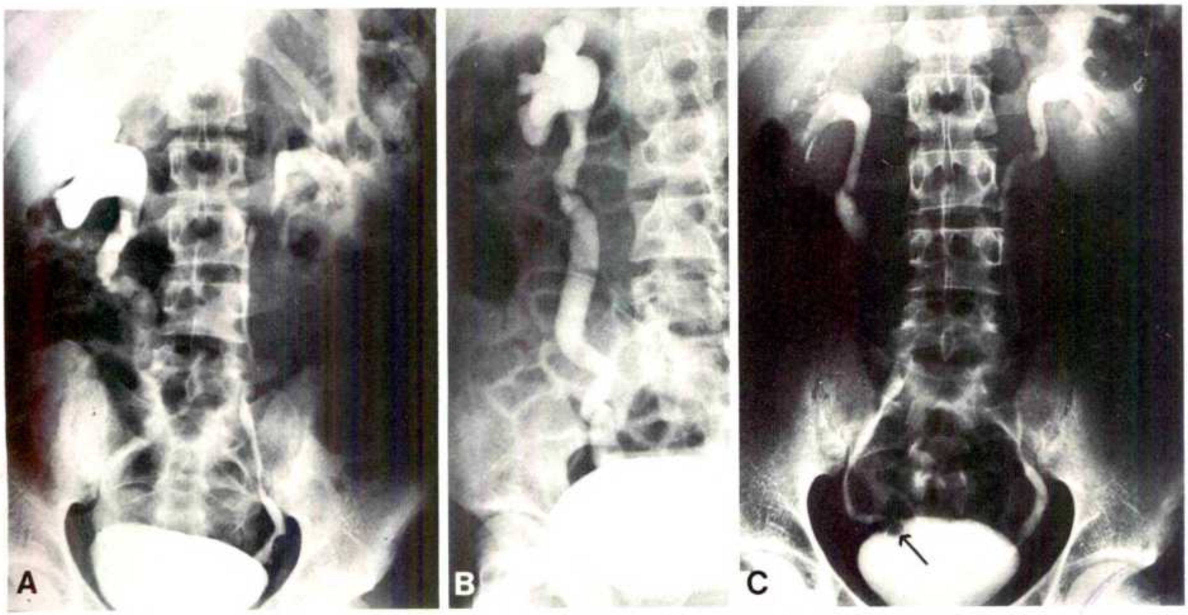

Fig. 3 (A) Grossly dilated and minimally tortuous right ureter of case 10 due to vesicoureteric stenosis. (B) Oblique view of the same ureter. (C) IVU 12 months after surgery. Arrow shows site of the nipple.

sity; the dilatation was limited to the pelvic segments in three cases, whilst the others were dilated along their entire length with associated moderate to marked hydronephrosis.

Technique of nipple construction (Fig. 1)

The bladder and ureters are exposed through a Pfannenstiel incision and the pelvic segment of the ureter is mobilised as far as its entrance into the bladder. The bladder is opened by a midline incision, the ureteric orifice circumcised and the intravesical ureter dissected free from the bladder. A nipple, not less than 2 cm but no longer than 2.5 cm, is constructed using the technique similar to that of Urquhart-Hay *et al.* (1977) with a few minor modifications; the nipple is constructed outside the bladder and to prevent unrolling, the everted edge is sutured to the outer ureteric wall before it is delivered into the bladder.

The dome and postero-superior surface of the bladder are dissected free of peritoneum. A disc of bladder wall corresponding to the diameter of the prepared nipple is excised close to the midline; the nipple is delivered into the bladder, anchored at four different sites and intubated.

Construction of Nipples in Ureters with Radiological Calcification

There were two patients with radiological calcification of both bladder and ureters in whom three nipples were constructed. No significant difficulty was experienced in the creation of a nipple in one patient. In the other patient the two nipples were constructed with great difficulty because a considerable length of the pelvic ureters contained a dense collection of calcified ova and had to be excised.

Results

All patients experienced total symptomatic relief after surgery. Marked involution of the dilated urinary tract (Figs. 2 and 3) was observed in the repeat urograms of all but one patient, this latter patient being the one with ureteric and bladder calcification in whom bilateral nipple reimplantation was very difficult; post-operatively he had vesicoureteric reflux on both sides. The symptomatic and radiological improvement was sustained in all cases throughout the entire period of follow-up, which on average was more than 22 months (range 14 months-3 years). There were no serious post-operative complications.

Discussion

These results leave little doubt as to the effectiveness of nipple reimplantation in the management of bilharzial ureteric strictures. Its technical simplicity, freedom from complications, potential for reflux prevention and excellent late results make it an ideal procedure for ureters without radiological calcification, and the outcome is not adversely affected by the extent of ureteric dilatation before surgery. Further experience is essential, however, before rejecting its use in ureters with radiological calcification.

Acknowledgements

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The Author

B Elem, FRCS, Consultant Urologist and Honorary Lecturer, Urology Unit, Department of Surgery, University Teaching Hospital, Private Bag RW1X, Lusaka, Zambia.

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A Physiological Approach to the Investigation of Chronic Urinary Retention

D. G. MACHIN, B. P. GARDNER, K. A. WOOLFENDEN, A. D. DESMOND and K. F. PARSONS

Urological Units, Royal Liverpool Hospital and Broadgreen Hospital, Liverpool

Summary—Twenty-six male patients with chronic urinary retention were investigated by self filling cystometry, followed by fast filling cystometry.

Fast filling cystometry tended to increase the end filling pressure and to indicate a smaller bladder capacity than did self filling cystometry.

Inadequate filling of the bladder may lead to an unrepresentative detrusor voiding contraction and an incorrect diagnosis of detrusor failure.

Fast filling cystometry masks detrusor instability, which may be a factor producing upper tract dilatation and renal impairment.

It is suggested that chronic retention of urine should be investigated by self filling cystometry.

Previous investigators of chronic retention of urine (Abrams *et al.*, 1978) reported abnormally high bladder pressures during medium fill cystometry, but did not find evidence of phasic unstable detrusor contractions. In another study (George *et al.*, 1983) it proved impossible to introduce more than 300 ml into the bladder during inflow cystometry despite the drainage of a very large volume of residual urine minutes earlier.

It has been established (Hawkes *et al.*, 1981) that in certain conditions, fast filling cystometry can produce a "hypertonic" trace with a pressure rise during filling of more than 15 cm H_2O, which is artifactual.

This study was undertaken to investigate the extent of artifact produced by standard fast filling techniques in patients with chronic retention.

Patients and Methods

A prospective study was carried out on 26 male patients, mean age 69 years (range 54-79), suffering from chronic urinary retention secondary to outflow tract obstruction. Chronic retention was diagnosed on the basis of a palpable or percussable bladder after voiding which retained at least 300 ml of urine (mean residual urine 1283 ml, range 500-2670).

Any patient with clinically apparent prostatic carcinoma, vesicourethral neuropathy or previous surgery to the bladder or outflow tract was excluded from the series.

Urodynamic investigation began with the patient voiding into a flowmeter in private, having been asked to attend with a full bladder. Fine manometer tubing (PTFE—external diameter 1.3 mm) was introduced into the bladder by "hitch hiking" on a spigoted 12 F PVC Jacques catheter, which was subsequently withdrawn without loss of residual urine. A similar manometer tube with the tip protected by the finger of a plastic glove was inserted into the rectal ampulla. Subtracted detrusor pressure was monitored continuously while the patient's bladder filled naturally. The filling phase of the test was carried out in the supine position except when the patient sat up to drink. At a normal desire to void, the patient stood and voided into the flowmeter with the pressure lines *in situ*. After voiding the patient resumed a supine position and the post-voiding detrusor pressure

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

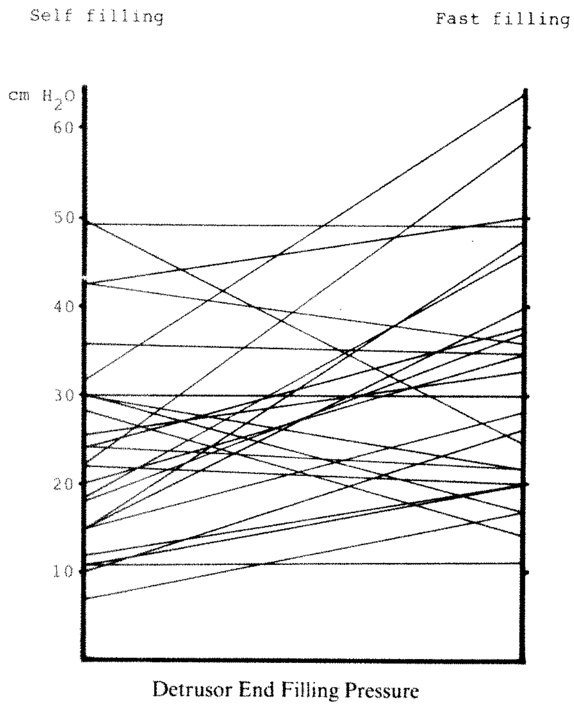


Fig. 1 End filling pressures tend to be higher on fast filling than on self filling ($P < 0.02$).

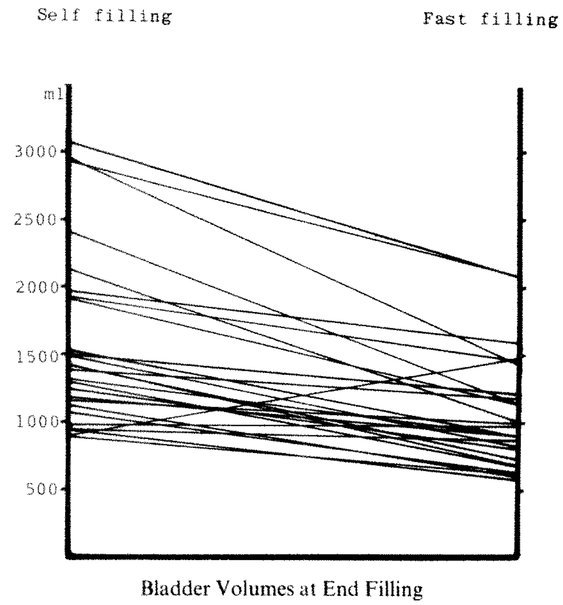


Fig. 2 End filling volumes are significantly greater on self filling than on fast filling ($P < 0.001$).

was monitored for 1 min. A 12 F catheter was passed to drain the residual urine.

Standard fast filling cystometry was then carried out using normal saline at room temperature. Saline was instilled into the bladder by gravity feed to the maximum tolerated capacity. The catheter was then removed and provocation testing performed (coughing, suprapubic tapping and heel bouncing). Thereafter the patient voided into the flowmeter once more with pressure lines *in situ*.

Results

On fast filling, the end filling detrusor pressures were significantly higher compared with self filling ($P < 0.02$) (Fig. 1). The end filling volumes were significantly greater ($P < 0.001$) after self filling (Fig. 2). The smaller end filling volume achieved by fast filling may lead to an inadequate detrusor voiding contraction (Fig. 3). Figure 3A shows that when the bladder was filled during self filling cystometry (bladder capacity 2964 ml) there was a detrusor voiding contraction of over 100 cm H_2O, which was sustained for 180 s. During fast filling in the same patient, the bladder capacity was only 1400 ml despite prolonged attempts to infuse a greater volume, and there was a weak and ill sustained voiding contraction (Fig. 3B).

Figures 4A and B show the end stage of filling in the same patient using self filling and fast filling respectively. Both traces were hypertonic but self filling cystometry clearly demonstrates unstable detrusor contractions which were not present with the fast filling technique.

In Figure 5 it can be seen that there is a significant difference in the incidence of detrusor instability between self and fast filling ($P < 0.01$).

Discussion

This study has demonstrated that fast filling cystometry can be misleading in a number of respects. In particular, it fails to provide accurate data on bladder pressures during filling or identify the presence of detrusor instability, which may be a significant factor in causing dilatation of the upper tract and renal damage (Machin *et al.*, unpublished data).

The bladder capacity achieved by fast filling cystometry was significantly lower than that produced by self filling, despite great care to instill the maximum possible volume of saline into the bladder. It should be noted that the end point of filling was different using the two techniques. Self filling cys-

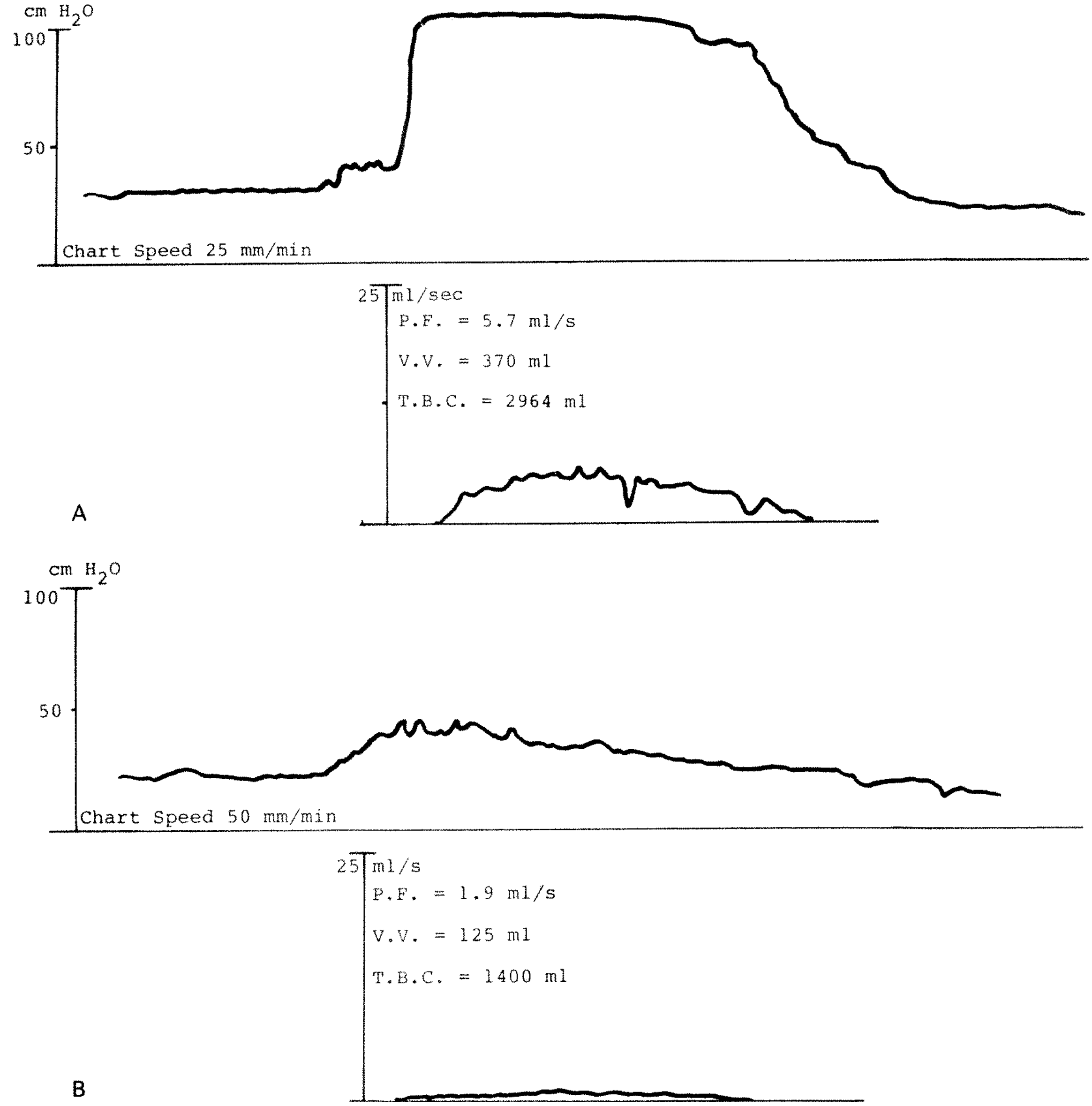


Fig. 3(A) Self filling trace showing the voiding phase. The detrusor voiding pressure exceeds 100 cm H_2O. **(B)** Fast filling trace showing the attempt to void at maximum tolerated capacity. There is a poor detrusor response with a detrusor voiding pressure of < 50 cm H_2O, which might suggest a degree of detrusor failure.

tometry was stopped at "desire to void", whereas fast filling cystometry was continued to the maximum tolerated capacity. Despite these different end points of filling the volumes achieved by fast filling cystometry were less than those observed during self filling. It was found that if fast filling was merely conducted to "desire to void" there was a poor detrusor response in the voiding phase. Under these circumstances it is impossible to determine whether this poor detrusor contraction is due to detrusor impairment or inadequate filling. However, if a bladder can be adequately filled by fast filling this will produce a representative detrusor voiding contraction.

Precise information about detrusor function preoperatively is vital since it will often determine further treatment if an apparently adequate operation to relieve outflow tract obstruction fails to cure the problem.

We believe that the results produced by self filling cystometry more closely reflect actual bladder activity and that it is the only satisfactory method

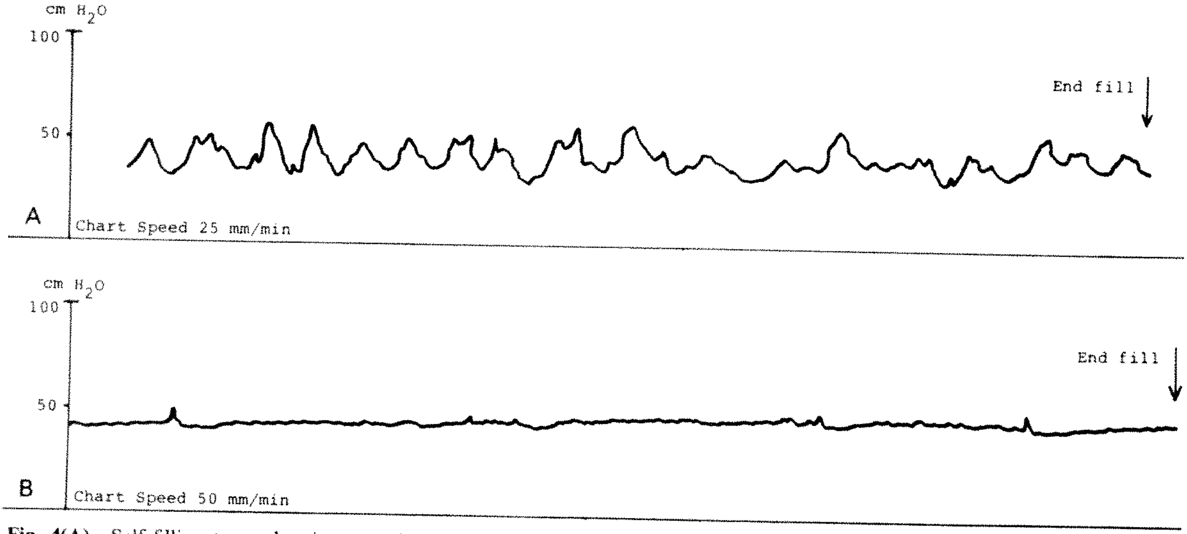
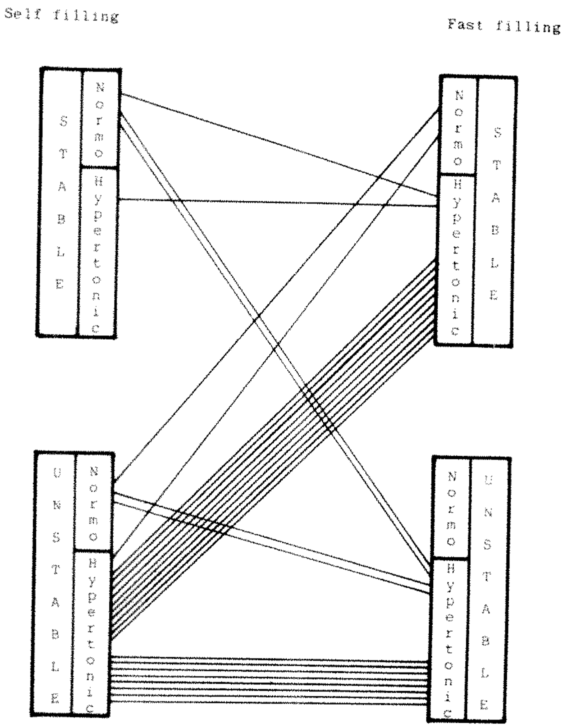


Fig. 4(A) Self filling trace showing unstable detrusor contractions in addition to hypertonicity. **(B)** Fast filling trace in same patient as 4A. Trace shows hypertonicity but there is no evidence of phasic unstable detrusor contractions.



Detrusor Activity during Cystometry

Fig. 5 There is a marked difference in the incidence of detrusor instability when self filling cystometry is compared with fast filling cystometry. (Chi-squared = 6.88, $P < 0.01$).

to predict post-operative performance. All cases of chronic urinary retention should be investigated by this means.

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The Authors

D. G. Machin, FRCS, MAKR Research Fellow and Honorary Senior Registrar, Royal Liverpool Hospital.

B. P. Gardner, MRCP, FRCS, Senior Registrar, Mersey Regional Spinal Injuries Unit, Promenade Hospital, Southport.

K. F. Woolfenden, FRCS, Senior Registrar in Urology, Royal Liverpool Hospital.

A. D. Desmond, FRCS, Consultant Urological Surgeon, Broadgreen Hospital.

K. F. Parsons, FRCS, Consultant Urological Surgeon, Royal Liverpool Hospital.

Requests for reprints to: D. G. Machin, Department of Urology, 9Z Link Unit, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

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Patterns and Significance of the Sacral Evoked Response (the Urologist's Knee Jerk)

N. T. M. GALLOWAY, G. D. CHISHOLM and A. McINNES

University Department of Surgery/Urology and Department of Clinical Neurophysiology, Western General Hospital, Edinburgh

Summary—Neurological examination may fail to demonstrate any abnormality in patients who have neurogenic bladder dysfunction. Standard clinical methods will include full examination of segmental nerves to the level of S1 but will not include the lower sacral segments which control sphincter function. We describe a simple method of measuring the integrity and function of these segments of the cord. The method and the common patterns of response are described. The stimulus is physiological (not supramaximal), the response is measured with surface mounted electrodes at the urethral and anal sphincters and each measurement is the average response after 100 stimuli.

In the investigation of suspected neurogenic bladder dysfunction, urologists continue to rely on the traditional diagnostic methods of cystography, cystometry and panendoscopy. At best these are indirect measures of nerve function. The findings that are consistent with neurogenic dysfunction are often non-specific and careful judgement is necessary unless gross abnormalities are present. Many urodynamic (Lapides *et al.*, 1962) and neurophysiological (Krane and Siroky, 1980; Bilkey *et al.*, 1983) investigations have been devised to help in the diagnosis of neurogenic dysfunction. Most are complex, difficult to perform and to interpret. There is a need for a simple, reliable method of measuring directly the integrity and function of the nerves to the lower urinary tract. The following is such a method.

Method

A urethral ring electrode (Disa 21L 11) is mounted on a 14 F Foley catheter 1 cm below the balloon for a female and 2.5 cm below, depending on the length of the prostatic urethra, in men. The catheter with its electrode is then passed after lignocaine gel anaesthesia and the balloon inflated. It is gently withdrawn until the balloon is at the internal meatus and the bladder is drained. The plug electrode is then passed into the anal canal and the earth electrode placed around the thigh. The EMG activity is recorded at rest, with gripping and with cough.

The hand-held stimulator is placed on the dorsum of the base of the penis/clitoris in the midline overlying the dorsal nerve. Using a stimulus of 0.1 ms duration and a frequency of 2/s, the magnitude of the stimulus is slowly increased from zero. The patient is asked to declare his first awareness of the stimulus—the sensory threshold. This is repeated until it is a consistent value (usually 4-8 mA). The stimulus is then increased slowly until the magnitude of the stimulus is 3 times threshold. The averaging mode is selected and the EMG activity of the anal and urethral muscle is independently averaged for each epoch of 100 ms after every stimulus. It is usually sufficient to record for just 1 min.

Random activity is eliminated by averaging but if an increase in EMG activity does occur in a constant temporal relationship to the stimulus, a response is measured. The latency is most simply measured to the peak of the response. The amplitude is the height of the response and is measured from peak to peak. The response is always repeated to confirm its reproducibility. It is important to start the stimulus from zero and increase slowly to 3 times threshold. This is much more comfortable

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Read at the 40th Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

for the patient and is well tolerated. If the same response is not obtained it must be repeated using a greater stimulus. If the response is absent the stimulus should be steadily increased and repeated at intervals up to the limit of the patient's tolerance.

A second useful response is obtained without any change in electrode positions. Instead of stimulating the dorsal nerve, the urethral electrode is connected to the stimulator unit and the sensory threshold of the urethra is recorded. It is important to repeat this measurement until it is consistent (normal 4-10 mA). Again the stimulus is increased slowly to 3 times threshold and the average response at the anal electrode is measured. The latency of this response is about 65 ms + 10 and to ensure that a late response is not missed, a sweep of 200 ms is used. The averaged response is recorded and repeated as before until there is a consistent response; if there is no response the stimulus is increased until a consistent response is found or it becomes too uncomfortable for the patient.

Pitfalls

If no response is found it is essential to check the electrical contacts and to ensure that the anal electrode has not been displaced. Excessive lubrication of the anal plug, a very lax anal canal or gross obesity may each contribute to poor contact and give a false negative response. If no urethral response is found the resting EMG pattern should be measured and a slight change in position of the electrode can be made to enhance the signal.

Significance

The normal response (Fig. 1) implies an intact sacral innervation. The normal latency of the response is 38 ms + 4 (N = 18). A delayed response (Fig. 2) is evidence of neurogenic dysfunction and implies delay in peripheral nerve conduction or delay between spinal interneurones or an abnormally long reflex arc length. This pattern is common in primary nocturnal enuretics and may also be found in diabetic or alcoholic patients with peripheral neuropathy. Absent response (Fig. 3) is usually evidence of profound neurogenic dysfunction. If the sensory threshold is normal an absent response implies a lesion of the interneurones within the spinal cord or a lesion of the motor neurones. Static EMG will give evidence of a significant motor neurone lesion. If the sensory threshold is greatly raised or there is no awareness of stimulation and the response is absent, the lesion is likely to involve the peripheral sensory pathway (afferent nerve or dorsal root). If the response is present but there is no awareness of stimulation, the lesion is likely to involve the ascending tracts or cerebral cortex. Any complete lesion of the afferent nerve,

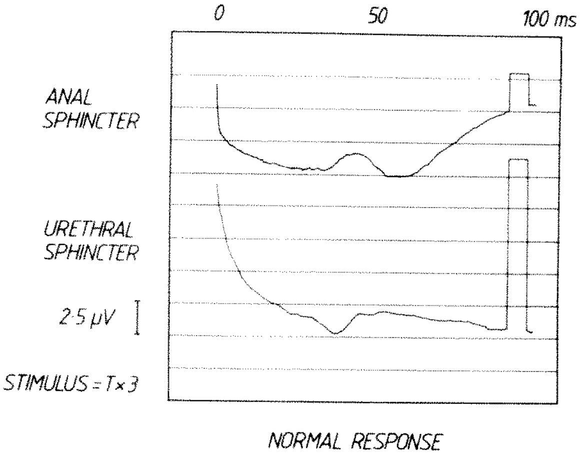

Fig. 1 Normal response (latency 38 ms + 4).

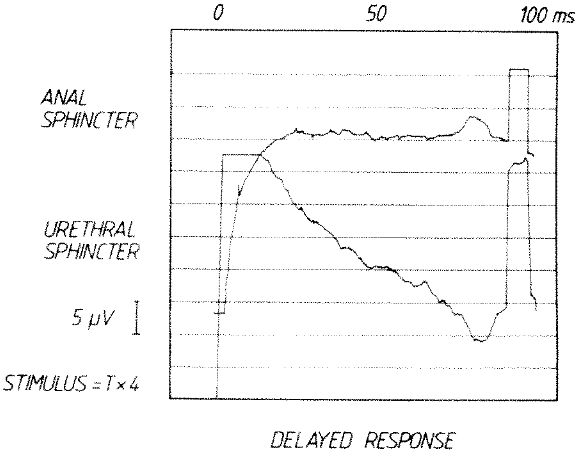

Fig 2 Delayed response (latency > 50 ms).

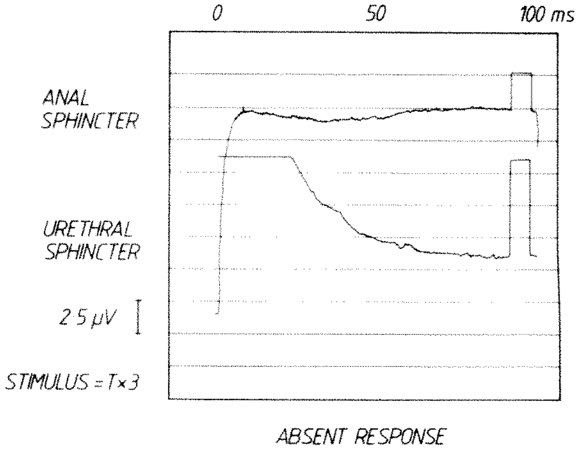

Fig. 3 Absent response.

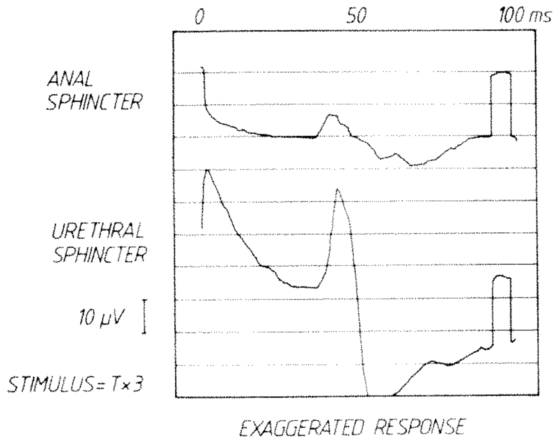

Fig. 4 Exaggerated (giant) response (amplitude > 100 µV).

interneurones or efferent nerves will result in an absent response. An exaggerated (giant) response (Fig. 4) is often found if there is an upper motor neurone lesion.

Discussion

This method has now been applied in 350 studies in 85 patients and has produced reliable and highly reproducible results. The time taken for a full study is about 15 min. The use of surface electrodes within the urethra and the anal canal permits the measurement of total sphincter activity from a constant electrode position. This solves the problem of accurate needle placement and is comfortable for the patient. If there is nerve damage some motor units within the muscle will be lost, some may be abnormal and others preserved and if the response is measured with a needle, the response will vary according to the precise location of the needle within the muscle. The total response measured with a surface electrode is constant and the sampling error which invariably occurs when a needle is used is avoided. Clearly, if there is no neurogenic damage and all the motor nerve territories within the muscle have an intact nerve supply, a constant response will be obtained with both the surface and needle electrodes.

The print-out of the average response is derived from the change in EMG activity and not the EMG itself. Our experience is based on the Disa 1500 EMG system and more recently on the Medelec MS92. Both are satisfactory but the Medelec instrument is readily portable and less expensive. Suitable equipment is already widely used in the investigation of neurological disease and is available in most hospitals.

Useful clinical data about the site of the neurological lesion are obtained from sacral evoked response measurements and recovery can be monitored by serial studies. One young patient presented with urinary retention and a small pelvic abscess after appendicectomy; the sacral evoked response was absent. The abscess resolved with conservative treatment and after 6 weeks a delayed response returned, he was managing without a catheter but still had some urinary difficulty. After 3 months the sacral evoked response was normal and his normal voiding habit was restored.

Six women with "psychogenic retention" have been studied and all had unequivocal neurogenic dysfunction (absent in 5 and profound delay in 1). These findings have influenced our selection of patients for further investigation with myelography and neurosurgical referral. Similarly, patients who developed urinary retention after laminectomy (3) or rectal surgery (4) have been studied and if the sacral evoked response is present, immediate outflow tract surgery is indicated. If the response is absent the patient is likely to have neurogenic retention which may not be relieved by prostatectomy. We would recommend deferring operation and repeating the response measurement after 4 weeks. Deferring operation will allow those patients who have evidence of neurological recovery to declare themselves and so avoid inappropriate outflow tract surgery.

Sacral evoked responses give a reliable measure of the integrity of sacral nerve arcs, but the technique must be applied with careful attention to detail.

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The Authors

N. T. M. Galloway, FRCS, FRCSE, formerly Lecturer, University Department of Surgery/Urology, Western General Hospital, Edinburgh. Now Senior Registrar, Department of Urology, Cardiff Royal Infirmary.

G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery, University of Edinburgh.

A. McInnes, MB, MRCP, Consultant Neurophysiologist, Western General Hospital, Edinburgh

Requests for reprints to: N. T. M. Galloway, Department of Urology, Cardiff Royal Infirmary, Newport Road, Cardiff.

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Monoclonal Antibodies to Detect A, B and H Blood Group Isoantigens in Superficial Transitional Cell Carcinoma of the Bladder: a Means of Predicting Invasive Recurrences

T. J. STEPHENSON, J. L. WILLIAMS and K. GELSTHORPE

Departments of Histopathology and Urology, Royal Hallamshire Hospital, Sheffield

Summary—Monoclonal antibodies to A, B and H blood group isoantigens (BGI) have been used in an indirect immunoperoxidase technique to study the expression of BGI in both normal and malignant transitional epithelium in patients of all blood groups.

BGI was detectable in all 15 biopsies of normal transitional epithelium and in 28 of 50 (56%) stage pTa and pTl transitional cell carcinomas of the bladder (TCCB). In the tumours failing to express BGI there was a 55% invasive recurrence rate at 5 years compared with 14% in those tumours expressing BGI. The difference was significant at the $P < 0.01$ level.

The recent availability of a monoclonal antibody to H isoantigen expressed in group O patients, in addition to monoclonal anti A and anti B, has made possible the inclusion of patients of all blood groups into a study using a standard immunoperoxidase technique without the need for specially processed biopsy material. The advantages of this technique compared with the earlier methods are discussed with reference to its possible role in identifying those patients at highest risk of developin invasive recurrence of their tumour.

Following the report by Decenzo *et al.* (1975) that superficial TCCBs which expressed BGI showed a lower rate of invasive recurrence compared with those in which BGI was absent, there has been considerable interest in the phenomenon of BGI expression in TCCB (Bishop, 1982). The initial studies employed the specific red cell adherence test (SRCA) which is developed from the mixed red cell agglutination test employed by Coombs *et al.* (1956) to detect BGI in various epithelia. In a review of the initial studies based on the SRCA test, Stein and Kendall (1982) noted an overall accuracy rate ranging from 60 to 93% in the ability of SRCA to identify patients who would later develop invasive recurrence of their TCCB.

Despite a growing body of evidence for the value of the SRCA test as a prognostic indicator in TCCB (Catalona, 1981), problems inherent in th technique have precluded its widespread adoptio (Askari *et al.*, 1981; Cooper and D'Elia, 1982) Performance of the test requires the difficul manoeuvre of washing the non-adherent red cell away from the tissue section and interpretation o the slides is a problem (Lange and Limas, 1980) The SRCA test shares with the indirect immunofluorescence test the disadvantage of yieldin material which deteriorates with storage, requirin photography for permanent records (Cooper an D'Elia, 1982). These problems can be overcome b adoption of the indirect immunoperoxidase technique, which has the advantage of permanent an more easily interpreted results together with lower incidence of false negative results in group patients (Flanigan *et al.*, 1983). The reproducibilit of this technique has been limited by variations i specificity found in conventional antisera togethe with the need to use a lectin (Coon and Weinstein

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1981) in detecting H isoantigen in TCCB from group O patients.

The availability of monoclonal antibodies (Mc Abs) produced by immunoglobulin-secreting mouse hybridoma cell lines (Kohler and Milstein, 1975) has made their use, as reliable antibodies of high specificity, possible in the immunoperoxidase technique in addition to their wider use in serology (Gatter *et al.*, 1984). One example of the serological use of Mc Abs has been their introduction within the Blood Transfusion Service as blood grouping antisera (Voak *et al.*, 1982). In this study, Mc Abs against A, B and H (expressed in patients of blood group O) BGI, originally developed for use in blood typing, are used as primary antibodies in a standard indirect immunoperoxidase technique to detect BGI expression in superficial TCCBs.

Patients and Methods

The series comprised 50 otherwise unselected patients who had presented with stage pTa or stage pTl (UICC, 1978) TCCB; they had had at least 5 years of regular follow-up supplemented by cystoscopic biopsy of recurrent tumours. Patients with less stringent follow-up and those dying from unrelated causes during the 5-year follow-up period were excluded. The blood groups of the patients are shown in Table 1.

Table 1 Blood Groups of Patients in the Study Group and of Patients Providing Control Biopsies

	A	*B*	*AB*	*O*	*Total*
Study group	24	8	1	17	50
Control cases	5	4	0	6	15

Table 2 Relationship Between Histological Grade (Koss, 1975) and Biological Behaviour of 50 Tumours

	No invasive recurrence at 5 years	*Invasive recurrence within 5 years*
Grade I or I-II	17	4
Grade II or III	17	12
Total	34	16

Fisher's exact probability test: $P > 0.05$, not significant.

The paraffin blocks (ranging from one to three per case) of the initial biopsies were retrieved. Table 2 shows the histological grades (Koss, 1975) of the tumours as originally reported, while the post-operative histopathological stages (UICC, 1978), determined by incorporating the operative cystoscopic findings, are shown in Table 3.

Table 3 Relationship Between Post-operative Histopathological Stage (UICC, 1978) and Biological Behaviour in 50 Tumours

	No invasive recurrence at 5 years	*Invasive recurrence within 5 years*
pTa	15	7
pTl	19	9
Total	34	16

x^2 test: $P > 0.05$, not significant.

Cystoscopic cup biopsies of normal transitional epithelium were obtained with informed consent from 15 patients during transurethral resection of the prostate for histologically proven benign prostatic hyperplasia. These were fixed for 24 h in 10% formal saline prior to embedding in paraffin wax for routine histological processing.

Controls

Five slides from each block were processed so that in addition to one slide being exposed to antibody appropriate to the patient's blood group, one slide was stained using each of the two antibodies inappropriate for the patient's blood group, one slide was treated with culture medium identical to that in which the hybridoma cell lines had been grown (Eagle's medium with 10% fetal calf serum) and one slide was treated with phosphate buffered saline (PBS). Within each batch of slides processed, sections of normal urothelium from patients of blood groups A, B and O were incorporated. Staining of vascular endothelium and surface of erythrocytes by the appropriate, but not by any inappropriate, antibody for the patient's blood group provided a valuable internal positive control in every section. The staining activity of each antiserum was absorbed out if it was incubated for 24 h at 4°C with erythrocytes of the relevant blood group.

Immunohistochemistry

Undiluted supernatant from stable cloned mouse hybridoma cella line 4-3-3-5 secreting anti-H (Trent Regional Blood Transfusion Centre), stan-

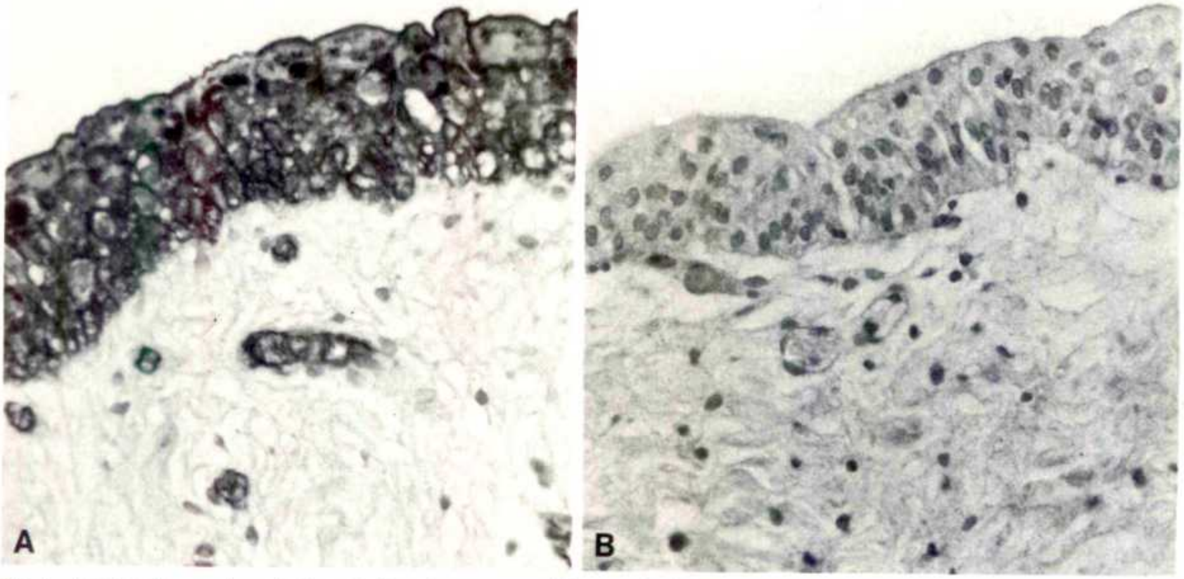

Fig. 1 Section of normal urothelium, indirect immunoperoxidase method photographed with blue filter (× 345), from patient of blood group O. (A) Application of anti-H Mc Ab results in staining of BGI in urothelium, vascular endothelium and on red cells. (B) Negative control using anti-B Mc Ab showing no staining.

dard monoclonal anti A and anti B (batch numbers 8382 and 9015 respectively, both distributed within the National Blood Transfusion Service by Oxford Blood Group Serology Reference Laboratory) were examined for specificity by slide agglutination tests with washed group O, A and B red cells. Sections cut at 5µ were deparaffinised and rehydrated prior to blocking endogenous peroxidase activity with 0.5% 100 volume strength hydrogen peroxide in methanol for 20 min. Mc Abs were diluted with PBS at pH 7.6 to give an agglutination titre with washed red cells of 1:256 and 200 µl of this diluted antibody was applied to the slides for 30 min at 20°C. After washing in PBS, sections were incubated with 100 µl rabbit anti-mouse peroxidase conjugate (Dakopatts), diluted to 1% in PBS containing 2% normal human serum, for 30 min. The sections were then rinsed and flooded with a fresh solution of diaminobenzidine and H_2O_2 (10 mg diaminobenzidine with 200 µl 30 volume H_2O_2 in 20 ml TRIS buffered saline at pH 7.6) for 10 min prior to washing and counterstaining with haematoxylin.

Results

BGI was demonstrable within the urothelium, the vascular endothelium and on the surface of red cells in each of the control biopsies (Fig. 1). There was no staining when Mc Abs inappropriate to the patient's blood group were applied.

Twenty-eight (56%) of the initial biopsies from the 50 patients presenting with superficial TCCB showed expression of BGI (Fig. 2) either throughout the tumour or, as a minimum, within the full extent of the basal layer of cells. Twenty-two (44%) of the cases showed total deletion of BGI expression (Fig. 3) evidenced by failure of any of the urothelium to stain in the presence of positive staining of vascular endothelium and erythrocytes in the same section.

The correlation between a tumour developing an invasive recurrence within the 5-year follow-up period and its BGI expression status is shown in Table 4. The chi-square test shows the difference between the 55% invasive recurrence rate in the BGI-negative and the 14% invasive recurrence rate in the BGI-positive tumours to be significant at the $P < 0.01$ level.

The invasive recurrence-free interval for the BGI-positive and BGI-negative groups was compared by the Mantel-Haenszel test for survivorship data (Peto *et al.*, 1977): the difference between the two curves is at the $P < 0.01$ level (Fig. 4).

The relationship between BGI expression and histological grade of tumour is analysed in Table 5; for simplicity, grades I and I-II and grades II and III (Koss, 1975) of tumours are grouped together.

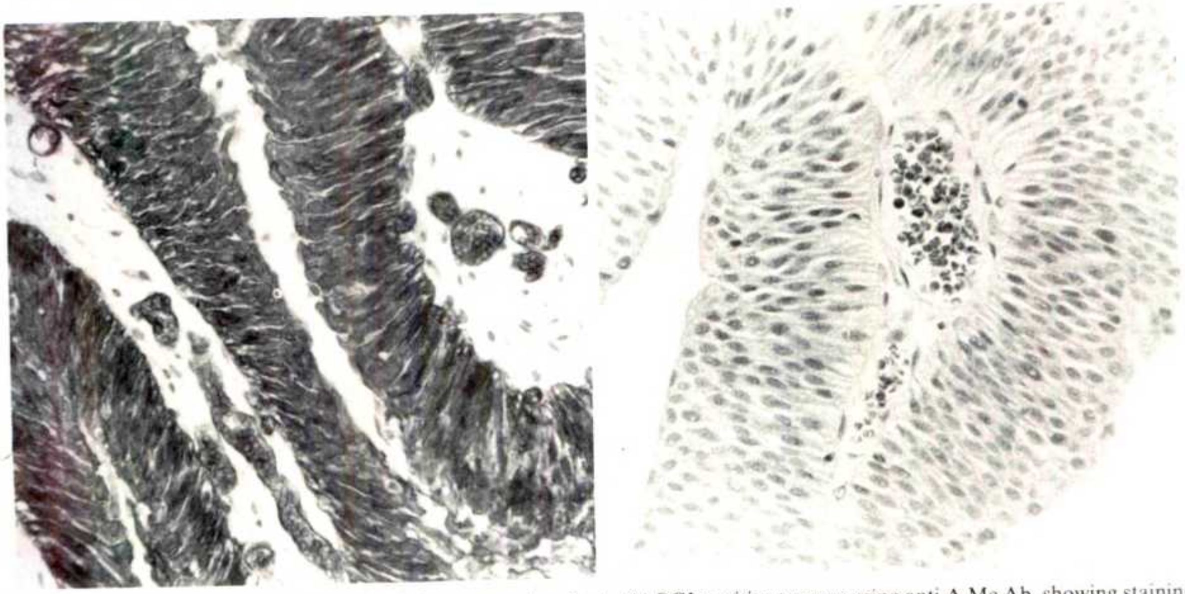

Fig. 2 Section of stage pTa TCCB (× 345) from group A patient. (A) BGI-positive tumour using anti A Mc Ab, showing staining throughout tumour. (B) Control section from same tumour using anti-H, showing absence of staining.

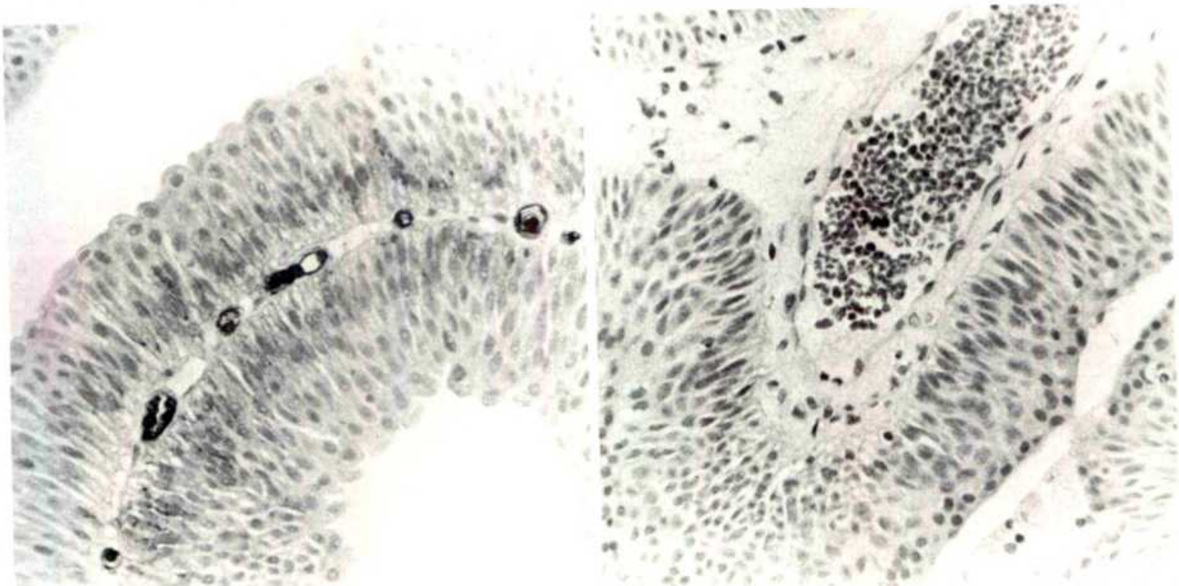

Fig. 3 Section of stage pTa TCCB (× 345) from group B patient. (A) BGI-negative tumour: anti B Mc Ab has resulted in failure of tumour to stain in the presence of positive staining of vascular endothelium and red cells. (B) Control section of same tumour: application of anti A Mc Ab gives no staining of any structure.

Calculation of the Kappa statistic of association (Cohen, 1960) shows that there was no significant association between tumour grade and BGI expression within this group of patients.

Discussion

The recent availability of Mc Abs to H isoantigen has made possible the inclusion of patients from all blood groups in this study where previously patients of blood group O have been excluded from study by Mc Abs (Finan *et al.*, 1982). The use of Mc Abs in immunohistochemistry confers the substantial advantages of absolute purity and well defined specificity compared with conventional polyclonal antisera; furthermore, future large scale

Table 4 Relationship Between Invasive Recurrence and Isoantigen Expression

	Isoantigen-positive	*Isoantigen-negative*	*Total*
No invasive recurrence	24	10	34
Invasive recurrence	4	12	16
Total	28	22	50
% with invasive recurrence	14%	55%	

$\chi^2 = 7.42$, $P < 0.01$.

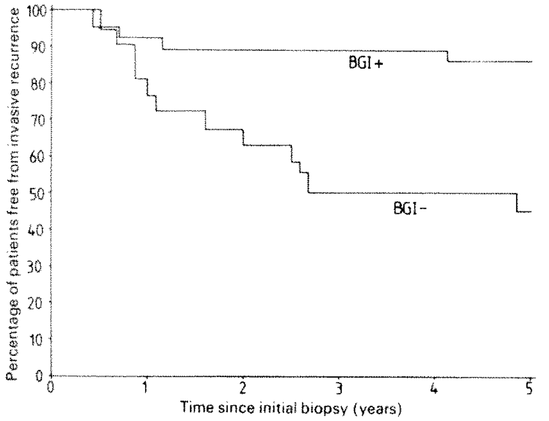

Fig. 4 The timing of invasive recurrences within the BGI-positive and BGI-negative groups. Mantel-Haenszel test, $P < 0.01$. $N = 50$.

Table 5 Relationship Between Histological Grade (Koss, 1975) of Tumour and Isoantigen Expression

	Isoantigen-positive	*Isoantigen-negative*	*Total*
Grade I or I-II	12	9	21
Grade II or III	16	13	29
	28	22	

Kappa statistic of association, $K = 0.02$, not significantly different from zero (Cohen, 1960).

production should make inter-laboratory comparison of results possible. These advantages are most apparent in the demonstration of H isoantigen in the urothelium of group O patients, where since the original observation by Decenzo *et al.* (1975) of BGI expression in TCCB it has become clear that conventional antisera are unsatisfactory for detection of H antigen. The problem has been partially solved by the use either of a lectin derived from *Ulex europaeus*, whether in the SRCA test (Askari *et al.* 1981; Coon and Weinstein, 1981) or by immunofluorescence (Kent, 1964), or by immunoperoxidase (Flanigan *et al.*, 1983). A novel alternative method has used antiserum from patients with Bombay blood, who develop antibodies against H isoantigen (Srinivas and Kiruluta, 1984). However, the method employed in our study offers the advantage that one standard immunoperoxidase technique can be used to incorporate patients of all blood groups.

While this study, which included 50 patients, was retrospective and made use of formalin-fixed and paraffin-embedded material up to 7 years old, the results, in terms of the ability of the loss of BGI expression to identify a group of patients at increased risk of developing an invasive recurrence of their tumour within the 5-year follow-up period, have achieved a high level of statistical significance (Table 4, Fig. 4). However, since established indices such as stage (UICC, 1978), grade (Koss, 1975) and multiplicity of tumours are already available to yield prognostic information (Williams *et al.*, 1977; Lutzeyer *et al.*, 1982), it is important to ask whether testing for BGI status gives any prognostic information beyond these routinely determined indices. In the context of our study, neither stage nor grade of the initial tumour biopsy yielded statistically significant prognostic information, yet there was a significant association between loss of BGI expression and development of invasive recurrence. It appears, therefore, that testing for tumour BGI expression may yield useful supplementary prognostic information beyond that obtained from the routine histological examination of biopsies.

For any predictive test, sensitivity and specificity can be defined thus:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives + false negatives}}$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives + false positives}}$$

If "positivity" is taken as deletion of BGI expression, and a "true positive" is a case where deletion of BGI has correctly predicted invasion, then analysis of the data in Table 4 shows that within the sample of 50 patients, absence of BGI expression in the initial tumour biopsy has a sensitivity of 75% in predicting future invasive recurrence within 5 years and a specificity of 71%. Both of these figures are too low for a predictive test to be adopted on its own as a basis of patient management. However, if the sample of patients in this study is representative of the population of patients presenting with superficial TCCB as a whole, it appears that determination of BGI expression by this technique may yield useful additional prognostic information beyond the routine histological examination. A large prospective study with a follow-up period of at least 5 years will be required to determine whether testing for BGI expression should have a role in patient management.

Acknowledgements

We are grateful to Professor L. Henry for his foundation of the record system, without which the cases could not have been studied, to Professor J. C. E. Underwood for critical reading of the text, to Miss P. Mills for advice on technical methods and to Mrs M. Hogg for typing the manuscript.

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The Authors

T. J. Stephenson, MA, MB, ChB, Registrar in Histopathology.

J. L. Williams, FRCS, Consultant Urologist.

K. Gelsthorpe, PhD, Principal Scientific Officer, Trent Regional Blood Transfusion Centre.

Requests for reprints to: T. J. Stephenson, Department of Histopathology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

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Minor Defects of the Sacrum and Neurogenic Bladder Dysfunction

N. T. M. GALLOWAY and J. TAINSH

University Department of Surgery/Urology and Department of Radiology, Western General Hospital, Edinburgh

Summary—Minor defects of the sacrum are common and often dismissed as normal. The radiographs of 100 patients with urinary incontinence revealed sacral abnormalities in 43. Sacral evoked responses were measured and compared independently with the radiological findings. Patients who had defective closure of the dorsal neural arches of S1 or S2 all had abnormal nerve studies. We suggest that incomplete development of the bones of the dorsal neural arches of the upper sacrum may be a marker of incomplete neurogenesis of the sacral nerves. The sacral neurological deficit is subtle and difficult to demonstrate, but it is real and may be important in the pathogenesis of incontinence.

Minor abnormalities of the sacrum are commonly seen on IVU and are usually disregarded. Many patients attending the incontinence clinic were noted to have minor radiological defects of the sacrum, particularly absence of the sacral dorsal neural arches. Most of these patients required full urodynamic investigation and this included sacral evoked response measurements. The results of these investigations were compared retrospectively with the radiological features which were assessed independently by a radiologist who was not aware of the clinical data.

Patients and Method

The radiographs of 100 patients attending the incontinence clinic were assessed by a radiologist (JT) who made a diagrammatic sketch of the dorsal neural arches of each and noted any other bony abnormality. Thirty-five patients who had a sacral anomaly were fully investigated using standard urodynamic techniques and all patients had sacral evoked response measurements. The radiological definition was too poor to allow accurate assessment of nine patients. Of the remainder, 48 were considered normal, but 43 had defective closure of the dorsal neural arches of the upper sacral segments. Eight patients with a sacral defect refused investigation or had insufficient symptoms to warrant it. Thirty-five patients had a full investigation. Their mean age was 34 years (range 14-63) and the female to male sex ratio was 3 : 1.

Results

The presenting complaints included noctural enuresis, frequency/urgency, urge incontinence, stress incontinence, and recurrent urinary infection. There was a past history of noctural enuresis in 48% of patients and a family history in 57%. The pattern of voiding was urgent and most admitted to some difficulty in voiding by volition. None of these patients had neurological disease and none had had surgery. Clinical examination included full neurological examination; saddle sensation and perineal reflexes were normal, but nine patients had some external stigma of dysraphism.

Urodynamics

Bladder sensation and awareness of filling were diminished in 54%. Synchronous videocystometry revealed phasic detrusor instability in 72% and

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

ureteric reflux was seen in 6%. Some patients had difficulty with voiding; 42% had relative outflow obstruction with poor relaxation of the external sphincter mechanism and relatively high voiding pressure. Sacral evoked responses were abnormal in 90%. The latency was prolonged in the majority but some responses were absent (urethra to anus absent in 18%).

Discussion

These patients were attending the incontinence clinic and all had symptoms of urinary dysfunction, but none had either symptoms or signs of neurological disease. Patients who had a defect of closure of the dorsal neural arches of the first or second sacral segment invariably had an abnormal response. It is concluded that so-called minor abnormalities of the sacrum may be associated with a significant, but unrecognised sacral neurological deficit. This nerve deficit may be the obstacle which blocks the emergence of normal voiding behaviour by day and a dry bed at night.

The Authors

N. T. M. Galloway, FRCS, FRCSE, formerly Lecturer, University Department of Surgery/Urology, Western General Hospital, Edinburgh. Now Senior Registrar, Department of Urology, Cardiff Royal Infirmary.

J. Tainsh, MB, ChB, BMedBiol, MRCP, DMRD, Registrar, Department of Radiology, Western General Hospital, Edinburgh.

Requests for reprints to: N. T. M. Galloway, Department of Urology, Cardiff Royal Infirmary, Newport Road, Cardiff.

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Pelvic Lymphadenectomy and Radical Cystectomy for Transitional Cell Carcinoma of the Bladder with Pelvic Nodal Disease

H. ZINCKE, D. E. PATTERSON, D. C. UTZ and R. C. BENSON, Jr.

Department of Urology, Mayo Clinic and Mayo Foundation, Rochester, USA

Summary—Past and present methods of treatment for patients with stage D_1 (T1-4 N+ M0) transitional cell cancer of the urinary bladder have proved to be largely ineffective. This report on 57 patients with stage D_1 disease confirms this impression and demonstrates that radical operation alone is associated with a 5-year survival rate of only 10%. Survival is related to tumour grade and to the number of pelvic lymph nodes involved; furthermore, complete lymphadenectomy may contribute to improved patient survival. Effective treatment programmes for stage D_1 bladder cancer are lacking and efforts should be directed toward developing treatment protocols that combine radical cystectomy and meticulous pelvic node dissection with an effective adjuvant systemic treatment programme.

The results of radical cystectomy with only nodal biopsy for transitional cell cancer of the bladder with pelvic nodal involvement (D_1; T1-4 N+ M0) continue to be discouraging. Radical surgery combined with complete pelvic lymphadenectomy for this stage may have some therapeutic value (Skinner, 1982), but additional reports on this subject are necessary. We present our results with radical cystectomy and pelvic lymphadenectomy (complete and partial) for transitional cell carcinoma of the urinary bladder with metastases to the pelvic lymph nodes.

Patients and Methods

From 1960 until 1980, 53 men and 4 women (age range 36-81 years; mean 63 years) with transitional cell cancer of the bladder and regional nodal involvement and no evidence of extrapelvic disease underwent pelvic lymphadenectomy and radical cystectomy with urinary diversion. Patients with non-transitional cell cancer who had node biopsy only were excluded from this review. All 57 patients were followed up from 2 years or more up to 20 years or death. Follow-up was complete and there were no other exclusions.

The operation consisted of removal of the distal common iliac, external iliac, hypogastric and obturator nodes bilaterally and radical cystectomy with urinary diversion. In this retrospective review we were unable to identify accurately those patients who had undergone a complete versus a partial pelvic lymphadenectomy. Thus patients were included in the group with complete lymphadenectomy when the total number of lymph nodes removed exceeded 10.

Patients were divided into four treatment groups: Group A, complete pelvic lymphadenectomy, one positive node (14 patients); Group B, partial pelvic lymphadenectomy, one positive node (18 patients); Group C, complete pelvic lymphadenectomy, two positive nodes (11 patients); Group D, complete pelvic lymphadenectomy, three or more positive nodes (14 patients).

Long-course (≥4500 rads) and short-course (≤2000 rads) radiation treatment had been given to 25 (43%) and 12 patients (21%) respectively before cystectomy and were evenly distributed

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Table 1 Pathological and Treatment Data

	*Group**				*Total*	
	A	*B*	*C*	*D*		
Pre-cystectomy radiation						
Long-course	5	9	4	7	25	
Short-course	5	4	1	2	12	
None	4	5	6	5	20	
Adjuvant treatment						
Radiation	5	1	2	1	9	
Chemotherapy	1	1	2	1	5	8 systemic
Both	0	0	2	1	3	
None	8	16	5	11	40	
Local grade						
1	0	0	0	0	0	
2	0	0	1	0	1	
3	9	14	4	9	36	
4	3	4	6	4	17	
None	2	0	0	1	3	
Local stage						
A/pT1	1	2	1	2	6	
B/pT2-3	4	4	3	1	12	
C/pT3b	7	12	7	10	36	
None/pT0	2	0	0	1	3	

* See text for description of patient groups.

among the treatment groups. Twenty patients (35%) did not receive pre-operative radiation (Table 1).

Local grade (1–4) and local stage (A-C, pT1–pT3) refer to surgical staging only and to the number of nodes.

Adjuvant treatment was given to 17 patients (radiation treatment ≥4000 rads or chemotherapy or both) (Table 1). Survival and non-progression curves were constructed by actuarial means (Kaplan and Meier, 1958) with regard to local grade, stage, number of nodes (one node, complete vs. partial lymphadenectomy; two nodes; and three or more nodes) and adjuvant treatment.

Results

There was no hospital mortality. Only 3 of the 57 patients (5.3%) are alive: 2 patients at 30 and 73 months after complete lymphadenectomy (one positive node) and one patient at 53 months after operation (four positive nodes). Of the 54 patients who died, 49 died of metastatic cancer and 5 died of causes not related to their primary disease 7, 7, 19, 43 and 65 months (mean 28.2 months) post-operatively.

Pre-cystectomy radiation and post-operative radiation or chemotherapy are listed according to patient group in Table 1. Only eight patients received systemic post-operative treatment (chemotherapy). Regarding the bladder itself, of note is the absence of grade 1 tumours; also, only one grade 2 tumour was found. The percentage of undifferentiated cancer was about evenly distributed, as was local stage. Most patients (63%) had local stage pT3b (C) tumours. Three patients did not have residual tumour after radiation therapy.

The 14 patients with one positive node and complete pelvic lymphadenectomy survived 4 to 73 months (median 28 months; mean 24 months). The 18 patients with one positive node and partial pelvic lymphadenectomy survived 2 to 79 months (median 18 months; mean 20 months). The 11 patients with two positive nodes survived 4 to 93 months (median 27 months; mean 20 months), and the 14 patients with three or more positive nodes

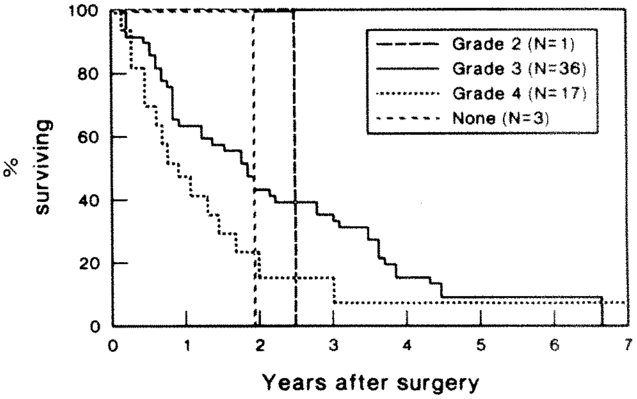

Fig. 1 Actuarial survival of 57 patients with carcinoma of bladder and nodal disease according to tumour grade of cystectomy specimen.

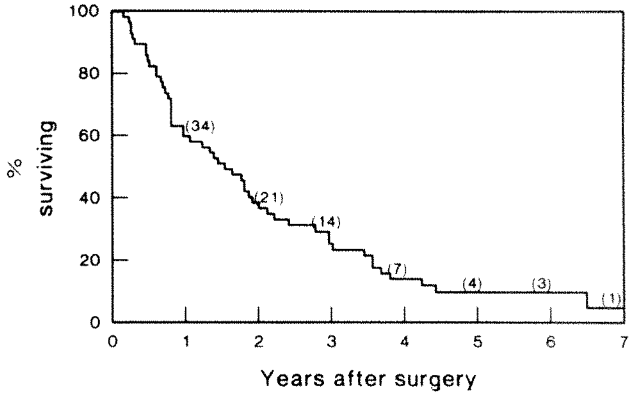

Fig. 2 Actuarial survival of 57 patients with carcinoma of bladder and nodal disease.

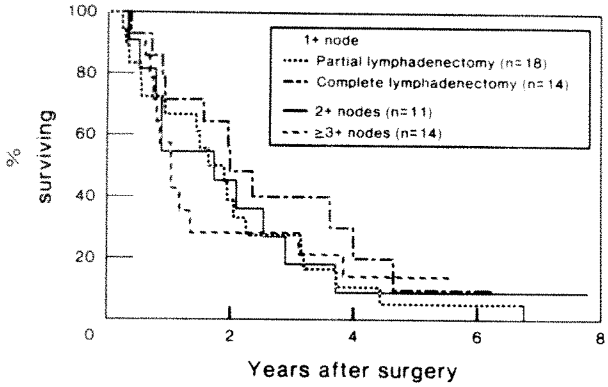

Fig. 3 Actuarial survival of 57 patients with carcinoma of bladder according to number of nodes involved and type of lymphadenectomy.

Table 2 Survival Rates With Pelvic Lymphadenectomy and Radical Cystectomy for Stage D_1

	No. of nodes	*No. of pts.*	*Survival ≥5 years (%)*
Whitmore and Marshall (1962)	≤2	13	16
Dretler *et al.* (1973)	≤2	12	33
	≤3	23	8.7
Laplante and Brice (1973)	?	39	12.8
Reid *et al.* (1976)	?	24	25.8
Smith and Whitmore (1981)	1-?	134	7
Skinner (1982)	1->10	36	36 (actuarial)
Present series	1->10	57	10 (actuarial)

survived 1 to 65 months (median 20 months; mean 11 months). Thus the number of nodes and complete lymphadenectomy seem to influence survival.

Of the other factors examined, tumour grade seemed to affect survival appreciably (Fig. 1) (but pre-cystectomy radiation, post-operative adjuvant treatment and local stage had no influence on progression or survival). However, patients with undifferentiated tumours also had a high incidence of multiple-node involvement.

Overall, 1-, 2- and 5-year actuarial survival rates were 60, 39 and 10% respectively (Fig. 2). When the individual subclasses of one node, two nodes, and three or more nodes were compared, patients with only one positive node had a slightly better survival rate. Patients with one positive node also had a more favourable survival curve if complete lymphadenectomy had been performed. Survival at 1, 2, 3 and 5 years for patients who had complete lymphadenectomy was 71, 48, 40 and 10% respectively; survival for those who had partial lymphadenectomy was 67, 33, 22 and 5% respectively (Fig. 3). Because non-progression curves were almost identical to survival curves, only the survival curves are shown. However, non-progression at 1 year for the 32 patients with one positive node was 65%, and non-progression for the 14 patients with three or more positive nodes was 17%.

Discussion

Our experience and that of others (Skinner, 1982) indicate that pelvic lymphadenectomy does not substantially increase the morbidity associated with pelvic surgery. We recommend that total pelvic lymphadenectomy should be included as part of the radical surgical removal of certain bladder cancers; among other purposes, it helps to identify patients who might benefit from adjuvant treatment. Previous reports (Whitmore and Marshall, 1962; Dretler *et al.*, 1973; Laplante and Brice, 1973; Reid *et al.*, 1976; Smith and Whitmore, 1981; Skinner, 1982) have attested to the feasibility of pelvic lymphadenectomy and radical cystectomy, which has provided 5-year survival rates ranging from 7 to 36% (Table 2). On the basis of these reports it seems that the number of nodes involved is a most important variable in predicting survival.

Variables such as what constitutes a complete pelvic lymphadenectomy (as interpreted by the individual surgeon) and attempts by the examining pathologist to find lymph node metastases are of significance and are difficult to quantify. It is possible that most of the poor results have followed node biopsy operation rather than meticulous node dissection, as demonstrated in a recent report (Skinner, 1982). Our series supports this theory (though not statistically): those patients who had one positive node and a complete lymphadenectomy fared better than those who had more nodes involved or who had a less complete lymphadenectomy.

It is remarkable that local progression did not develop in any of our patients and seemed to be independent of the use of pre-operative radiation (Smith and Whitmore, 1981). Rather, it seemed that the first mode of progression was associated with distant metastases in all patients. Furthermore, whether or not pre-operative radiation treatment had been used seemed to have no relation to survival. Too few patients (eight) had received adjuvant systemic treatment to allow any conclusions to be drawn. In our study of the other variables, local tumour grade, the number of nodes involved and complete lymphadenectomy seemed to affect survival results.

Although worldwide experience with radical surgery for transitional cell cancer of the bladder with lymph node involvement is limited, the results presented suggest the possibility of improved survival for patients with limited nodal involvement. That surgery should still be an integral part of treatment for stage D_1 disease is confirmed by the poor results obtained with exploration alone and by the occasionally significant morbidity associated with a retained bladder. Survival results in patients with limited nodal disease who undergo radical surgery with meticulous lymph node dissection may be improved by concomitant systemic chemotherapy. Appropriate prospective adjuvant effective treatment programmes (chemotherapy) need to be designed in order to improve our present dismal results.

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The Authors

H. Zincke, MD, Consultant in Urology, Mayo Clinic and Mayo Foundation; Professor of Urology, Mayo Medical School, Rochester.

D. E. Patterson, MD, Consultant in Urology, Mayo Clinic and Mayo Foundation; Instructor in Urology, Mayo Medical School.

D. C. Utz, MD, Consultant in Urology, Mayo Clinic and Mayo Foundation; Professor of Urology, Mayo Medical School.

R. C. Benson, Jr., MD, Consultant in Urology, Mayo Clinic and Mayo Foundation; Associate Professor of Urology, Mayo Medical School.

Requests for reprints to: H. Zincke, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

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Ileocaeco-urethroplasty after Total Cystectomy for Bladder Cancer

E. ALCINI, M. VINCENZONI, A. DESTITO, A. D'ADDESSI and G. C. CASTIGLIONI

Urological Division, Department of Surgery, Catholic University of the Sacred Heart, Rome, Italy

Summary—Eleven cases of ileocaeco-urethroplasty, performed over a 2-year period, are presented. The patients had low grade bladder cancer infiltrating into but not extending beyond the muscle layer (B-T3a). Following radiotherapy a total cystectomy was performed up to the verumontanum; afterwards the prostatic cuff was anastomosed to an ileocaecal segment.

The patients have been followed up for 13 to 39 months. One died from metastases after 30 months. The others are alive and in good psychological condition, with satisfactory micturition. We believe this surgical option deserves more careful consideration.

More than 30 years after Couvelaire first suggested using the intestinal tract to replace part or the whole of the bladder, enterocystoplasty is still criticised by many workers (Charghi *et al.*, 1967; Sullivan *et al.*, 1973; Durand *et al.*, 1975; Kvarstein *et al.*, 1980). We report our experience with an ileocaeco-urethroplasty which we consider to be a good alternative to other forms of urinary diversion.

Patients and Methods

Between June 1980 and August 1982 11 male patients underwent cystoprostato-vesiculectomy and ileocaeco-urethroplasty for bladder carcinoma. They were selected according to the criteria of Camey and Le Duc (1979). They were under 70 years of age and free from serious disease which might have increased the risk of post-operative complications. The tumours did not infiltrate beyond muscle (B or T2-T3a) and were moderately differentiated (I-II according to Koss (1975)). The regional nodes were clinically negative and the tumour was extra-trigonal in order to avoid the risk of urethral spread (Table 1).

The operation was usually preceded by a week's radiotherapy, to a total of 2000 rads. We perform a total cystectomy (*i.e.* a cystoprostato-vesiculectomy, cutting the urethra just below the verumontanum) but we do not do a wide lymphadenectomy. After removing the whole bladder, the seminal vesicles and almost all of the prostate, an anastomosis is made between the prostatic cuff and the ileocaecal segment, which consists of caecum, an abundant portion of ascending colon and the last 7 to 8 cm of terminal ileum (Gil-Vernet, 1965) (Figs. 1 and 2). Vicryl sutures were used for the anastomosis.

At follow-up 3 months post-operatively, a bone scan (and if necessary X-rays), liver function tests, intravenous urography (Fig. 3), voiding cysto-urethrography (Fig. 4) and sequential renal angioscintigraphy were carried out and repeated every 6 months thereafter. Some patients also underwent urodynamic testing. Urine cultures were done frequently and infection treated immediately.

Results

Two months after the operation six patients were satisfactory. Three patients had urinary fistulas following removal of the catheter and two had a

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Table 1 Summary of Cases

	Age	*Sex*	*Stage*	*Grade*	*Location*	*Follow-up (months)*	*Progression (metastases)*
1	60	M	B1-T2	II	Right lateral wall	39	No
2	53	M	B2-T3a	II	Dome	30	Yes (dead)
3	62	M	B2-T3a	II*	Right lateral wall	34	No
4	56	M	B2-T3a	II	Left lateral wall	32	Yes
5	49	M	B2-T3a	II	Left lateral wall	28	No
6	53	M	B2-T3a	II	Right lateral wall	25	No
7	61	M	B2-T3a	I	Dome	21	No
8	64	M	B2-T3a	II	Right lateral wall	20	No
9	59	M	B2-T3a	II	Dome	18	No
10	61	M	B2-T3a	II	Right lateral wall	15	No
11	67	M	B2-T3a	II	Left lateral wall	13	No

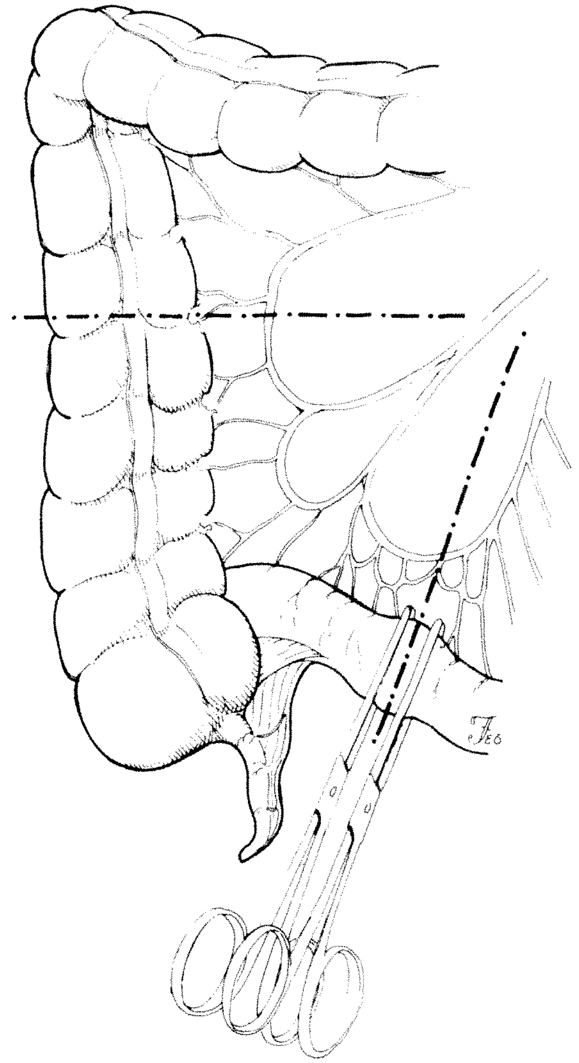

Fig. 1 Dotted lines show the ileocaecal segment employed together with the ileocolic artery.

urinary fistula with pelvic abscess (Table 2). At least 12 months after operation one patient has a non-functioning kidney but enjoys good health and has overall normal renal function. Sixteen months post-operatively another patient complained of pain at the site of the caeco-urethral anastomosis. CT scan showed the probable presence of a 3-cm metastasis in the obturator lymph nodes and this was confirmed by biopsy. Radioactive iodine seeds were implanted into the neoplastic tissue and the patient is now alive and well. One patient developed vertebral and hepatic metastases and died 30 months post-operatively. Another developed unilateral low pressure vesicoureteric reflux but retained normal renal function.

Urodynamic evaluation has been carried out in recent cases no more than 10 weeks after removal of the urethral catheter and again after stabilisation of micturition some 4 to 6 months post-operatively.

Table 2 Post-operative Evaluation

After 2 months

Good (6 patients)
- ureteric catheters removed after 15-17 days
- urethral catheter removed after 21 days
- discharge from hospital after 25-30 days

Complicated (5 patients)
- 3 temporary urinary fistulas after catheter removal*
- 2 urinary fistulas with pelvic abscess*

After more than 13 months

1 death after 30 months from metastases
1 metastasis in the obturator nodes treated with ^{125}I seeds
1 obstructed kidney
1 low pressure vesicoureteric reflux

* Fistulas developed between caeco-urethral anastomosis and skin.

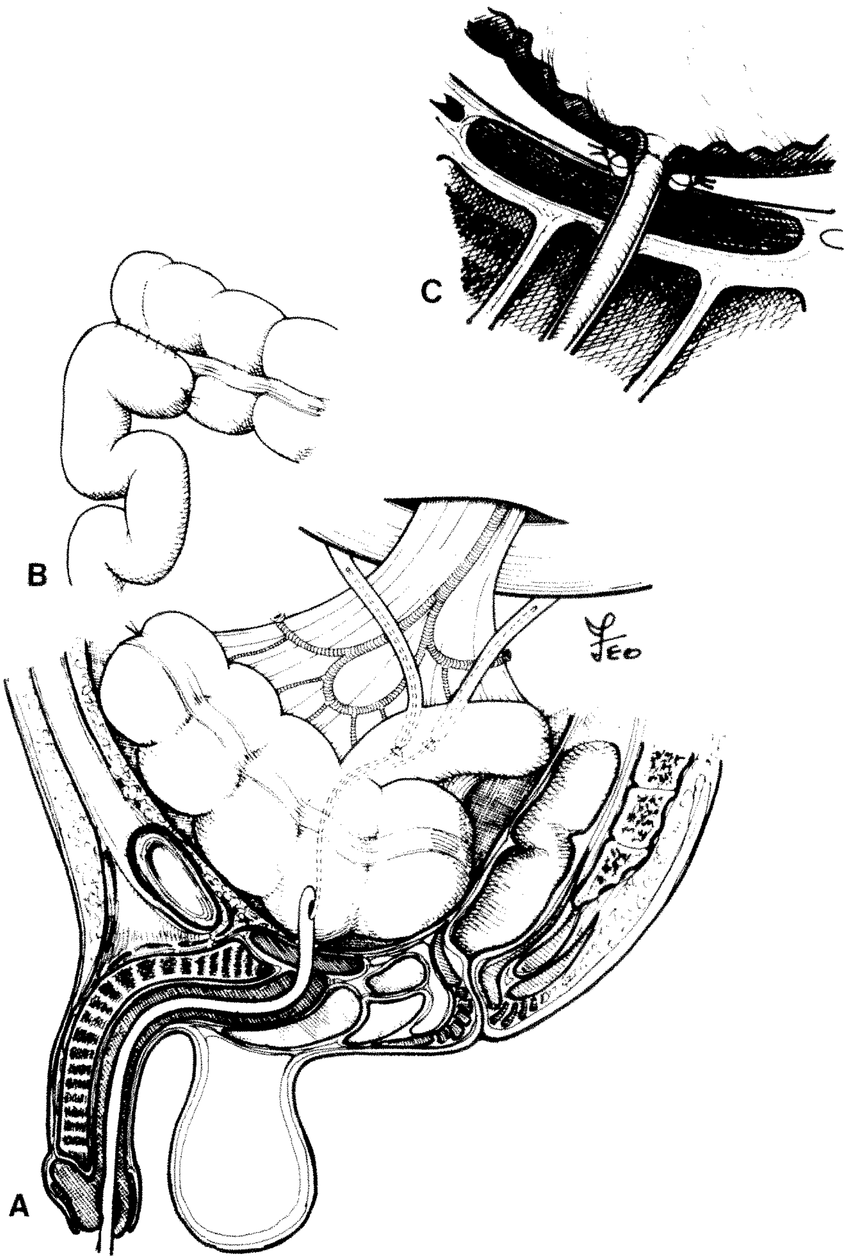

Fig. 2 Ileocaeco-urethroplasty. (A) Details of drainage at end of operation. (B) Ileo-transverse anastomosis. (C) Caeco-urethral anastomosis using the least amount of prostatic cuff.

A good functional result was 3 to 4 times micturition by day; a satisfactory result was a good urinary stream and a residual urine of < 70 ml.

Two patients complained of enuresis during sound sleep but prefer to use devices similar to those used by paraplegics rather than waken periodically.

Discussion

The capacity of the new bladder varies between 250 and 350 ml. The patient may have to urinate every 30 min soon after removal of the urethral catheter but this gradually improves to 3 to 4 h. Our patients, like others already reported (Camey and

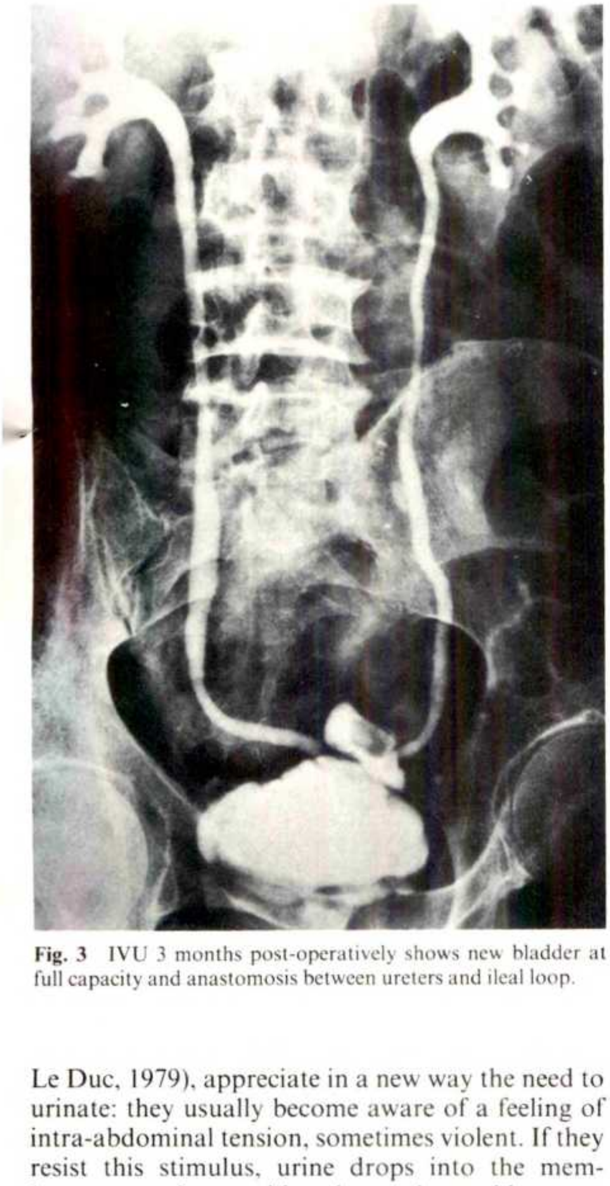

Fig. 3 IVU 3 months post-operatively shows new bladder at full capacity and anastomosis between ureters and ileal loop.

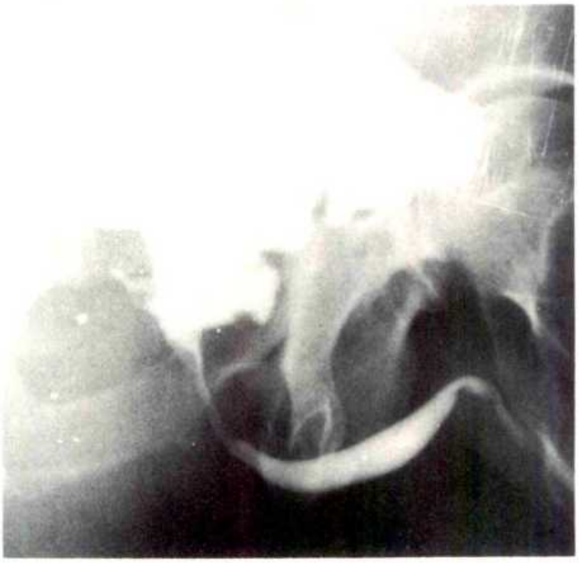

Fig. 4 Same patient as in Figure 3. Voiding cystography confirms lack of vesicoureteric reflux.

Le Duc, 1979), appreciate in a new way the need to urinate: they usually become aware of a feeling of intra-abdominal tension, sometimes violent. If they resist this stimulus, urine drops into the membranous urethra, making the need to void urgent. By relaxing the perineal musculature and contracting the abdominal muscles, however, the patient almost always has time to suppress micturition and to empty his bladder when he chooses. This phase can be seen clearly in the urodynamic test. Patients find that various positions (sitting, crouching or standing) seem to help them to empty the bladder.

This technique, unlike others, gives the patient the psychological and functional benefits of voluntary micturition and fulfils all the criteria of radical oncology.

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The Authors

E. Alcini, MD, Head of Urological Division.

M. Vincenzoni, MD, Assistant Professor, Department of Radiology.

A. Destito, MD, Assistant, Department of Surgery.

A. D'Addessi, MD, Resident, Department of Surgery.

G. C. Castiglioni, MD, Head of Department of Surgery.

Requests for reprints to: Dr A. D'Addessi, Via della Balduina 210, 00136 Rome, Italy.

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Ejaculation and Sexual Function after Endoscopic Bladder Neck Incision

H. HEDLUND and A. EK

Department of Urology, University Hospital, Lund, Sweden

Summary—Endoscopic incision of the bladder neck, performed to relieve outflow obstruction, was evaluated as regards effects on ejaculation and orgasm in 61 men (mean age 48 years) by analyses of seminal fluid and a questionnaire. Relief of obstruction was confirmed by post-operative normalisation of urinary flow. In 47 cases there was unchanged antegrade ejaculation, while reduced semen volume was reported by 11 men and retrograde ejaculation by only 3. The quality of orgasm and sexual satisfaction were not permanently changed by the operation. Post-operative analysis of seminal fluid was performed in 27 patients, with normal results in 26. In 16 men who provided specimens both before and after bladder neck incision, no consistent change was found in the semen. An incision completely splitting the bladder neck but not extending distal to the verumontanum will relieve outlet obstruction. Maintenance of antegrade ejaculation can be expected in most patients undergoing this operation.

Transurethral incision of the bladder neck to relieve outflow obstruction is an old concept (Guthrie, 1834). It was revived with the development of transurethral diathermy in the early 1930s, when Beer (1933) recommended "incision of the internal sphincter at 5 and 7 o'clock with the point electrode, using the high frequency current". Since the report by Turner-Warwick *et al.* (1973) on bladder neck dysfunction and its treatment by endoscopic diathermy incision, this has become the method of choice in various types of outlet obstruction.

Transurethral incision has been described as a preferable alternative to transurethral resection in younger men with symptoms of a small, "trapped" prostate (Orandi, 1973; Turner-Warwick *et al.*, 1973; Edwards and Powell, 1982). Other circumstances in which the endoscopic incision may be useful are bladder neck obstruction accompanying urodynamically verified detrusor failure or decompensation with increased residual urine and reduced flow rate (Jenkins and Allen, 1978). The operative technique is simple and few immediate complications have been reported (Turner-Warwick *et al.*, 1973). A possible sequel, however, is retrograde ejaculation. As younger men in particular are selected for the operation, preservation of fertility is important.

Investigations of the post-operative ejaculation status have hitherto been confined to questioning the patients (Keitzer *et al.*, 1961; Orandi, 1973; Jonas *et al.*, 1979; Turner-Warwick, 1979; Andersen *et al.*, 1980; Moisey *et al.*, 1982; Delaere *et al.*, 1983), and no analyses of seminal fluid have been reported. The results of earlier studies are summarised in Table 1.

The present study was undertaken to obtain more substantial documentation concerning ejaculation and sexual function following endoscopic incision of the bladder neck. In addition to completing a questionnaire, patients provided semen for analysis.

Patients and Methods

The study comprised 61 men, mean age 48 years (range 24-64) who between 1975 and 1983 underwent endoscopic incision of the bladder neck

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Table 1 Retrograde Ejaculation after Endoscopic Bladder Neck Incision in Previous Studies

Year of report	*Authors*	*Retrograde ejaculation (%)*	*No. of patients asked*
1961	Keitzer *et al.*	"temporary"	not stated
1973	Orandi	"temporary"	not stated
1979	Turner-Warwick *et al.*		
	bilateral incision	15	not stated
	unilateral incision	5	not stated
1979	Jonas *et al.*	7	103
1980	Andersen *et al.*	0	28
1982	Moisey *et al.*	16	26
1983	Delaere *et al.*	37	11

because of outflow obstruction, though not from prostatic hyperplasia. Five of the men complained of some erectile dysfunction, but in the others penile erection and ejaculation had been normal. (Five additional patients were operated on, but were excluded from the study because of advanced age and low level of libido).

Uroflowmetry (Siemens-Elema, Uro-Mini®) was done before and after the operation in all 61 men. Simultaneous pressure-flow studies were also done in 20 men. Micturition cystourethrography was performed before surgery in 50 cases and also afterwards in 8. The bladder neck was incised bilaterally in 32 patients and unilaterally in 29. The incision was deep, down to the perivesical fat, running from the trigone to the verumontanum at 4 and/or 8 o'clock. Catheter drainage was routinely removed within 48 h after the incision.

Post-operative seminal fluid was later on obtained by masturbation from 27 men in the Fertility Laboratory. Pre-operative semen had been delivered by 16 of the same men. A questionnaire concerning micturition, ejaculation and sexual function was answered by all 61 patients 6 months or more after endoscopic incision.

Results

Urinary function was improved by endoscopic incision in all cases. Normal micturition was confirmed by maintained rate of maximum urinary flow in all patients (Table 2). In two patients the primary incision failed because of inadequate surgical technique, but a second attempt was successful soon after the first.

Of the 27 post-operative samples of seminal fluid, 26 were found to be normal. In the other patient the semen was judged to be pathological because its volume was less than 1 ml and total sperm count 10 million. The fructose content could not be measured in this specimen. In the 16 patients whose fertility was studied both before and after the operation, there was no consistent change in specimen volume, sperm count or fructose content (Table 3). Qualitative factors—sperm morphology and motility—were within normal limits.

Table 2 Maximum Flow Rate (ml/s) in 61 Men Treated with Endoscopic Bladder Neck Incision (Means ± SEM)

	Post-operative			
Pre-operative	*3 months*	*1 year*	*2 years*	*≥4 years*
8.6 ± 0.5 *n* = 61	24.8 ± 1.5 *n* = 56	22.2 ± 1.5 *n* = 40	20.8 ± 1.6 *n* = 25	20.9 ± 1.3 *n* = 20

Table 3 Analyses of Seminal Fluid in 16 Men Before and After Endoscopic Bladder Neck Incision* and in Normal Controls (Mean ± SEM)

Semen	*Pre-operative*	*Post-operative*	*Controls (range)*
Volume (ml)	3.1 ± 0.3	3.6 ± 0.7	2-6
Sperm count (1×10^6/ml)	94.8 ± 15.3	90.6 ± 24.8	40-250
Fructose (mmol/l)	15.2 ± 0.4	19.0 ± 2.8	≥8

* Seven were operated upon by unilateral incision.

Unchanged ejaculation was reported in 47 of the 61 replies to the questionnaire (Table 4). The amount of seminal fluid was stated by 11 men to be consistently reduced, and three had no antegrade ejaculate. In one of these three, retrograde ejaculation was confirmed by analysis of urine voided after masturbation. As regards sexual function, only the three with retrograde ejaculation com-

Table 4 Ejaculation Capacity in 61 Men Following Endoscopic Bladder Neck Incision

	No. of patients
Unchanged, antegrade ejaculation	47 (21)
Diminished semen volume in antegrade ejaculation	11 (6)
Retrograde ejaculation	3 (0)

(Figures in brackets = no. with post-operative sperm analysis) plained of impaired sensation of orgasm. This disturbance diminished, however, and all three reported sexual satisfaction, despite failure of ejaculation, at check-up 6 months later. Five patients reported incomplete erectile ability, but these were the five who were pre-operatively examined for this reason.

Of the 47 men with unchanged, antegrade ejaculatory function, 21 delivered semen for analysis, and in all cases the quality was normal. Of the 11 who post-operatively experienced reduction in semen volume, six provided a specimen. The volume was subnormal in all six, but in five the quality was within normal limits.

Discussion

This study deals with 61 sexually active men in whom deep incision of the bladder neck was transurethrally performed to relieve symptoms of outflow obstruction. The effectiveness of the procedure as regards normalisation of the urinary flow is evident from Table 2.

Although all 61 men replied to the questionnaire, post-operative spermograms were achieved in only 27. In accordance with our routine, fresh sperm samples were obtained by masturbation.

Many patients find this procedure embarrassing, and semen for analysis was supplied chiefly by the younger patients and by middle-aged men still concerned about fertility. Unwillingness to masturbate in hospital and lack of incentive were the most probable reasons (rather than inability due to retrograde ejaculation) why patients declined to provide semen for analysis.

The questionnaire disclosed that 3 patients (5%) experienced retrograde ejaculation post-operatively, whereas 58 still had antegrade ejaculation. In this respect our results were comparable with most of those published by other investigators (Table 1).

Previous studies, unlike ours, did not include semen analyses. Normal ejaculate is composed of secretions from the prostate (13-32%) and seminal vesicles (46-80%) in addition to spermatozoa (*c.* 10% of the volume) from the ampulla and the vas deferens (Jenkins *et al.*, 1978). Reduced semen volume following bladder neck incision was found in 2 of 28 men by Andersen *et al.* (1980) and in 4 of 26 by Moisey *et al.* (1982). Six of our 11 patients who reported reduced semen volume post-operatively provided semen for analysis. Although the diminution in volume was confirmed, the spermograms—like those from the other post-operative specimens—showed semen quality within normal limits, but specific evaluation of the prostatic contribution was not included in our analysis.

Since no consistent change was found when both pre-operative and post-operative semen was obtained, our findings strongly suggest preserved fertility in patients with antegrade ejaculation maintained after incision of the bladder neck. We do not know, however, if any of the men have fathered children after the operation.

In healthy men antegrade ejaculation is assumed to be guaranteed by further tightening of the normally closed bladder neck. This contraction is mediated by sympathetic nerves from the thoracolumbar outflow (Learmonth, 1931). Retrograde ejaculation is often found after extensive lumbar sympathectomy (Rose, 1953) and after damage to the sympathetic fibres in patients undergoing retroperitoneal lymph node dissection (Narayan *et al.*, 1982) or excision of the rectum (Goligher, 1951). Diabetic neuropathy (Green *et al.*, 1963), alpha-adrenoceptor blocking agents (Green and Berman, 1954) and noradrenaline-depleting drugs (Schierger and Gifford, 1962) are other causes of retrograde ejaculation. Per-oral alpha-adrenoceptor stimulators may temporarily relieve retrograde ejaculation after retroperitoneal lymph node dissection (Narayan *et al.*, 1982).

Why some men have retrograde ejaculation after incision of the bladder neck, whereas most still have normal antegrade ejaculation, is not clear. In the present study the bladder neck was completely divided and the perivesical fat was discernible in the base of the incision. We found the same low incidence of retrograde ejaculation after unilateral as after bilateral incision. Post-operative cystography in several of the patients with preserved antegrade ejaculation showed an opened bladder neck. Ability to contract the bladder neck therefore does not seem *per se* to be a prerequisite for antegrade ejaculation. This view is supported by the finding of preserved antegrade ejaculation after Y-V urethrocystoplasty (Koraitum and Al-Ghorab, 1970) and in many patients who had undergone transurethral or suprapubic prostatectomy (Rieser, 1961).

Among previous investigators (Table 1), Delaere *et al.* (1983) reported retrograde ejaculation in 4 of 11 patients. These authors alone recommended that the incision should be extended distal to the verumontanum. In our patients the incision was usually stopped proximal to the verumontanum. This was not done primarily to prevent retrograde ejaculation, but because we do not believe that extending the incision below the bladder neck deep into true prostatic tissue gives any additional relief of outflow obstruction. As the ejaculatory ducts open distally to the verumontanum, it seems reasonable to deduce that after incision into the bladder neck the closure of the proximal urethra, and thereby antegrade ejaculation, is preserved by contraction of undamaged, smooth urethral musculature at the level of the verumontanum. This concept is consistent with previous studies of innervation and receptor function of the human urethra, in which the adrenergic nerve distribution and the contractile response of smooth muscle to adrenoceptor stimulating agents were found to be similar in the whole extent of the prostatic urethra (Ek *et al.*, 1977a, b).

We conclude that transurethral, unilateral or bilateral incision of the bladder neck consistently relieves outflow obstruction. Maintenance of fertility may be expected in the great majority of men who undergo this procedure. In order to relieve obstruction and preserve antegrade ejaculation, the incision should completely split the bladder neck, but should not be extended further distally than is necessary.

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The Authors

H. Hedlund, MD, Senior Registrar.
A. Ek, MD, Associate Professor.

Requests for reprints to: H. Hedlund, Department of Urology, University Hospital, S-221 85 Lund, Sweden.

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Transurethral Resection of the Prostate and Bladder Neck Incision: a Review of 700 Cases

L. E. EDWARDS, T. E. BUCKNALL, M. R. PITTAM, D. R. RICHARDSON and J. STANEK

Department of Urology, Westminster Hospital and Medical School and St Stephen's Hospital, London

Summary—Transurethral resection (TUR) is regarded as the treatment of choice for relief of outflow tract obstruction in the male, but bladder neck incision (BNI) is an acceptable alternative when the gland is small.

Seven hundred cases of TUR/BNI have been reviewed (TUR = 388; BNI = 312). BNI was performed when the gland was less than 35 g and where there was no clinical suspicion of malignancy. The operative details of our single incision technique are given.

While the patients in the BNI group were younger, catheter stay was shorter, there was less infection, a significantly reduced need for blood transfusion and a satisfactory outcome in terms of control and need for further surgery.

BNI is a technically simpler procedure than TUR and is easy to teach and learn. Results show it is safe and effective for patients in acute retention as well as those treated electively and it is the operation of choice for small benign prostates.

Transurethral resection (TUR) is generally accepted as the best treatment for symptomatic benign prostatic hypertrophy in all but the largest glands (Blandy, 1978). However, TUR is a skilled procedure and inexperienced or infrequent operators may be unable to match the good results and low complication rates reported from specialist urological units (Singh *et al.*, 1973; Chilton *et al.*, 1978).

Bladder neck incision (BNI), originally described by Bottini in 1887 and recently advocated by Edwards and Powell (1982), is a simple, quick and safe procedure for relieving outflow obstruction when the prostate is small and benign. Three hundred and twelve patients underwent BNI between October 1977 and March 1984. The results and complications of these procedures are compared with those in the 388 patients with larger benign glands treated by TUR over the same period of time.

Patients and Methods

Seven hundred men with outflow obstruction due to benign prostatic hypertrophy were treated by endoscopic surgery under the care of one consultant urologist (LE) between October 1977 and March 1984. All patients were assessed by clinical examination, a full blood count, urea and electrolyte estimations, urine analysis and intravenous urography. The choice of surgical procedure was made after cystoscopy and bimanual examination under anaesthesia. The criteria for performing bladder neck incision were a small benign prostate (35 g or less) and a relatively short prostatic urethra. Patients with larger prostates or a long prostatic urethra were treated by TUR. Where there was any clinical suspicion of malignancy the initial procedure was limited to cystoscopy and prostatic biopsy (Edwards, 1984).

Three hundred and twelve men were treated by BNI and 388 by TUR. The BNI patients were younger (mean age 62.8 years, range 32-83) than those in the TUR group (mean age 70.4 years, range 51-87).

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Bladder neck incision

Epidural, spinal or general anaesthesia without paralysis or intubation all proved satisfactory. Patients were placed in the semilithotomy position and examined bimanually and endoscopically. The decision to perform BNI or TUR was made on the findings of this examination. Urethrotomy to 32 F was performed with an Otis urethrotome. A resectoscope was passed and, using the Storz diathermy knife (27040 F or L), a cut was made along the sulcus in the 7 o'clock position from the right ureteric orifice to the level of the verumontanum. The cut was deepened to fat along its whole length. Only minimal haemostasis was required in most cases. The resectoscope was withdrawn and a Porges 22 F 3-way irrigating catheter (Code 3682-422) inserted on a curved introducer. The balloon was inflated with 30 ml of sterile water. Irrigation was continued with the glycine pre-operatively until the container in use was exhausted, when normal saline was substituted.

Transurethral resection

Anaesthesia was similar except that patients given a general anaesthetic were usually paralysed and ventilated. The instrumentation was similar to that used for BNI except that a cutting loop (27040 F or G) was fitted instead of a knife. The technique employed was that described by Blandy (1978). After the resection, a Porges 3-way catheter was inserted and irrigation continued as described above until the urine was a "rosé" colour, usually for 24 h.

Catheter management

After TUR the catheter was removed when the urine had become clear, usually on the second or third post-operative day.

Although the urine usually cleared rapidly after BNI the catheter was not removed until the fifth day in the first 102 cases. A different policy was subsequently adopted and the catheter was removed as soon as possible post-operatively, frequently on the first post-operative day.

Clinical monitoring

Results of cultures from midstream urine samples taken before operation and after removal of the catheter were recorded. Broad spectrum pre-operative antibiotic cover was given to patients with pre-existing urinary infections and to patients coming to theatre with an indwelling catheter. Blood transfusions were given in theatre at the discretion of the anaesthetist, and post-operatively the patients' haemoglobin was less than 10 g/l.

The major complications are recorded in Table 1.

Table 1 Complications

	BNI	*TUR*
No. of patients	312	388
Post-operative deaths	0	3 (0.77%)
Clot retention requiring return to theatre	4 (1.28%)	9 (2.3%)
Perforation and extravasation requiring return to theatre	2 (0.64%)	7 (1.8%)
Septicaemia	7 (2.2%)	20 (5.15%)
Incontinence: 6/52	12 (3.9%)	16 (4.12%)
1 year*	1 (0.32%)	6 (1.5%)
Further procedures	5 (1.6%)	7 (1.8%)
Others: Orchitis Stricture DVT Pneumonia	4 (1.28%)	9 (2.32%)
Total	23 (7.37%)	63 (16.2%)

* Excluding 109 patients where details were not available.

All patients were reviewed 6 weeks after discharge from hospital. Continence was assessed at this time, and at subsequent follow-up when necessary. Our definition of incontinence included minor degrees of urge incontinence and dampness.

The number and nature of further procedures undertaken were recorded.

Results

Pre-operative urinary infection rates were similar in the two groups (BNI 12.8%, TUR 13.14%). Post-operatively there was a small difference (BNI 19.9%, TUR 24.2%). Only five patients (1.6%) who had a BNI required a blood transfusion; they received an average of 2.0 units per patient transfused. Seventy-six patients (19.6%) were transfused during or after TUR; the mean volume of blood per patient transfused was 2.67 units.

Reference to Table 1 shows that there were three post-operative deaths following TUR; one patient died of myocardial infarction 7 h post-operatively, another of a massive pulmonary embolus 26 h post-operatively, and the third at 6 days from bronchopneumonia related to the large doses of Heminevrin required to control alcohol withdrawal. No patient died after BNI.

The details of the number of days of post-operative catheterisation and hospital stay in each group are given in Table 2.

Table 2 Clinical Details

	BNI		*TUR*
No. of patients	312		388
Age			
(Mean: years)	62.8		70.4
(range)	32–83		51–87
Post-operative catheter (mean: days)			
cases 1-102	4.3	2.01	3.23
103-312	1.9		
Post-operative stay (mean: days)			
cases 1-102	6.1	5.34	7.34
103-312	5.07		
Weight (mean: g)	nil		56.7
Resected (range)			8-123
Transfusion:			
No. of patients	5 (1.6%)		76 (19.6%)
Units/patients transfused	2.0		2.67
Urinary tract pre-op.	40 (12.8%)		51 (13.14%)
Infection post-op.	62 (19.9%)		94 (24.3%)

Up to the present time, five patients initially treated by BNI required a further procedure. This was another BNI in three patients who were considered in retrospect to have had an inadequate BNI initially. The other two patients had a TUR, one because of inaccurate assessment of prostatic size, and the other because of a substantial increase in prostatic size (89 g were resected 6 years after BNI). Seven patients initially treated by TUR required further surgery. Three have had a BNI for stenosis, and four had a further TUR for regrowth.

Discussion

This series cannot be a randomised study as criteria for admission to the two groups were entirely different. It does, however, set the results and complications of bladder neck incision against those of transurethral resection, the latter performed on patients with larger prostates on the same unit and during the same period. The results of TUR are comparable with those of the two large series from the London Hospital (Singh *et al.*, 1973; Chilton *et al.*, 1978).

Bladder neck incision is a technically simpler procedure than TUR and is easy to teach and learn. We feel that the results show that it is a safe and effective treatment for outflow obstruction in patients with small benign prostates. In this series BNI proved equally satisfactory for patients in acute retention and for patients treated electively.

We employed a single incision technique, in contrast to the double incision advocated by Turner-Warwick (1979) and Delaere *et al.* (1983). The importance in the single incision technique of a long, deep cut extending to perivesical fat along the whole length is illustrated by the three patients who required a repeat BNI after an initially inadequate incision. Despite the deliberate perforation, it proved possible to remove the urethral catheter as early as the first post-operative day. Control of voiding was regained rapidly, and the post-operative stay for BNI patients was significantly shorter than after TUR. Only one patient was rendered permanently incontinent after BNI.

Retrograde ejaculation is said to be less common after BNI than after TUR, although there is little objective evidence (Blandy, 1982). Orandi (1973) reported no sexual disturbance in a series of 40 patients treated by unilateral bladder neck incision. Delaere *et al.* (1983) noted retrograde ejaculation in 4 of 11 patients treated by bilateral incisions, while Moisey *et al.* (1982) reported 16% retrograde ejaculation after a single incision. Turner-Warwick (1979) considered that retrograde ejaculation was less common after unilateral incision (5%) than after bilateral incision (15%). Our earlier study (Edwards and Powell, 1982) reported figures similar to those of Moisey *et al.* (18%). We have found it very difficult to assess this aspect of sexual function as many of the patients do not appear to be aware of ejaculation or otherwise—some report that it remains normal, others that it is "reduced", and others consider that it is retrograde. We think it likely that our previous report of 18% is a conservative estimate and would suggest a figure nearer 35%, which does not seem unreasonable considering the length and depth of the myotomy which we employ. If these figures appear disappointing following the earlier reports, they should be compared with the virtual certainty of retrograde ejaculation following a properly performed TUR. While impotence resulted from none of the 700 procedures undertaken, one patient undergoing TUR regained his sexual prowess to an extent that complaints from his wife were forthcoming.

One potential disadvantage of BNI is that recurrent outflow obstruction may be more common than after TUR. In the present series further surgery was required more frequently after TUR than after BNI (1.8% compared with 1.6%), while some 3% of patients undergoing TUR in the London

Hospital series had second operations. The maximum follow-up in the present series approaches 7 years, while the minimum is as short as 3 months. However, our overall figures suggest that BNI appears comparable with TUR in the relief of obstruction due to a small benign prostate, provided that case selection is correct and the procedure is undertaken as described.

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The Authors

L. E. Edwards, MA, MChir, FRCS, Consultant Urologist.
T. E. Bucknall, MS, FRCS, Senior Registrar.
M. R. Pittam, MS, FRCS, Senior Registrar.
D. R. Richardson, RAF, FRCS, Senior Registrar.
J. Stanek, FRCS, Registrar.

Requests for reprints to: L. E. Edwards, Department of Urology, Westminister Hospital, Dean Ryle Street, London SW1P 2AP.

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Flutamide Therapy for Advanced Prostatic Cancer: a Phase II Study

J. R. MacFARLANE and D. A. TOLLEY

Department of Urology, Royal Infirmary, Edinburgh

Summary—A non-steroidal antiandrogen (flutamide) was used to treat 17 patients with advanced prostatic cancer. Twelve of 14 patients who had already failed to respond to conventional hormone therapy were dead within 12 months of starting flutamide therapy and there was a high incidence of side effects. Of three patients who had not received prior hormone therapy, two showed an early partial response and one showed no evidence of response to therapy.

Suppression of testicular androgen production in patients with prostatic cancer is usually achieved by orchiectomy or oestrogen therapy. However, continuing production of unsuppressed adrenal androgens may contribute to the failure of primary hormone therapy and thus cancer cells which were formerly hormone-dependent may still respond to secondary endocrine therapy. Many drugs have been used for this purpose, including corticosteroids, aminoglutethimide and cyproterone acetate, but in most cases only a short lived subjective improvement occurs and evidence of objective response is unusual (Muller and Hinman, 1954; Jacobi *et al.*, 1980).

Jacabo *et al.* (1976) reported that the palliative effect of flutamide was equal to that of stilboestrol in patients with advanced prostatic cancer and Stoliar and Albert (1974) demonstrated a response to treatment with flutamide in 7 of 18 patients whose disease had escaped from primary hormone control. Flutamide, a non-steroidal and weak antiandrogen, is believed to act by inhibiting androgen uptake or inhibiting nuclear binding of androgen in target tissues (Neri *et al.*, 1972; Peets *et al.*, 1974). It is therefore devoid of direct hormone activity and should be free of the side effects associated with other forms of androgen deprivation.

We undertook an open, non-randomised study to determine the efficacy and safety of flutamide for advanced prostatic cancer, both as primary treatment and in patients whose tumour had failed to be controlled with conventional hormone therapy.

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Patients and Methods

Seventeen patients were studied (mean age 74; range 59-85 years). All had either symptomatic bony metastases or documented evidence of disease progression before receiving flutamide therapy. Eight patients had already undergone orchiectomy and six had previously received stilboestrol; a further three received flutamide as primary treatment for their prostatic cancer. Patients were staged clinically according to the TNM classification (UICC, 1978) and a subjective assessment was based on performance status (WHO), pain score and a record of analgesia requirements. Various biochemical, haematological and radiological investigations were performed before and during flutamide therapy (Table 1). Informed written consent to participation in the trial was obtained from each patient. Patients received flutamide tablets 250 mg 3 times daily.

Patients were seen at 1 week and 3 weeks to check compliance and to record side effects. Responses were assessed at 3-monthly intervals from the start of treatment.

Results

The objective response to flutamide in those

Table 1 Parameters Measured Before and During Treatment

	Reviews				
Pre-treatment investigations	*3 weeks*	*3 months*	*6 months*	*12 months*	*15 months*
Acid phosphatase	√	√	√	√	√
Urea, electrocytes, Hb, WCC, platelets, LFTs	√	√	√	√	√
Chest X-ray	—	—	√	√	—
IVU bone scan	—	√	√	√	√

patients who had failed previous hormone therapy is shown in Table 2. Only one showed a temporary partial response at 3 months. In five patients, disease progression appeared to be halted at 3 months but all but one showed early evidence of disease progression. Of five patients who died within 6 months, four died of metastatic disease and one of a myocardial infarction. Six patients were withdrawn from the study, one because of rapid disease progression, the others because of intolerable side effects which stopped on withdrawal of flutamide therapy. Thus only one patient was alive at 12 months with stable disease.

Table 2 Objective Response (EORTC Response Criteria)

	Follow-up interval			
Response	*3 months*	*6 months*	*12 months*	*15 months*
Partial response	1	—	—	—
No response	5	2	2	1
Progression	1	2	1	2
Died	4	1	—	—
Withdrawn	3	2	1	—
Total	14	7	4	3

When flutamide was given as primary therapy, two patients showed an early response, and this was sustained for 18 months in one case. One patient is alive and well with stable disease at 15 months.

Eight patients showed a subjective response at 3 months but this was not sustained during follow-up.

Table 3 lists the side effects, all of which occurred within the first 3 months of treatment. Severe depression occurred in four patients, necessitating withdrawal of flutamide therapy in two. In these patients the mental state rapidly returned to normal on stopping the drug. Nausea and vomiting was the most common side effect and required withdrawal of treatment in two patients. One patient developed painful gynaecomastia.

Table 3 Toxicity to Flutamide

Side effects (11 patients)		*Withdrawn*
Severe depression	4	2
Nausea and vomiting	6	2
Dizziness	2	—
Rash	1	1
Gynaecomastia	1	—
Total	14	5

Discussion

The lack of measurable metastases in prostatic cancer makes assessment of new treatment difficult. However, in this study flutamide therapy does not appear to prolong survival in patients whose tumour has escaped from primary hormone control.

Although the National Prostatic Cancer Project considers that the survival of patients showing signs of partial regression and stable disease is similar to that of patients demonstrating progression (Slack *et al.*, 1980), we do not consider that the concept of stable disease should be used as a method of assessing the anti-cancer activity of a drug. Thus in our study only one patient was shown to have a partial objective response to therapy, although disease stabilisation appeared to occur in six patients. In most of these cases the stabilisation was short-lived and should not be regarded as evidence of response.

The incidence of side effects in 11 of 17 patients, together with the lack of objective evidence of response, make it unlikely that flutamide has any useful part to play in the palliation of hormone-escaped prostatic cancer. Furthermore, the presence of side effects may preclude its use as primary hormone treatment.

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The Authors

J. R. Macfarlane, FRCS, formerly Senior Registrar in Urology, Royal Infirmary, Edinburgh. Now Consultant Urologist, Victoria Hospital, Kirkcaldy.

D. A. Tolley, FRCS, Consultant Urological Surgeon.

Requests for reprints to D. A. Tolley, Department of Urology, Royal Infirmary, Edinburgh EH3 8YW.

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The Control of Male Stress Incontinence by Implantable Prostheses

J. W. FOWLER and C. D. AULD

Department of Urology, Royal Infirmary, Edinburgh

Summary—Twenty-six patients were treated by implantable prostheses in a 10-year period, 22 by primary Kaufman III and four by primary Rosen. Sixteen of 22 patients having the Kaufman III procedure were cured or markedly improved over a follow-up period of 6 months to 10 years. The Rosen prosthesis, whilst simple to install and making the patient continent, eventually produced urethral fistulae in all cases. The Kaufman III prosthesis appears to be the procedure of choice in uncomplicated male stress incontinence.

Stress incontinence in the male is a rare condition. It may follow injury to the prostato-membranous urethra and its supporting tissues (as at prostatectomy), following direct trauma to the bony pelvis and pelvic diaphragm, or remotely as a result of sacral cord or pelvic nerve injury and associated sphincteric weakness.

Treatment of this disabling condition by crural plication or by the implantation of solid acrylic or rib into the perineum has met with success only in the most experienced of hands (Kaufman, 1972). In 1973, however, Kaufman reported the results of the Kaufman III static appliance and later Scott *et al.* (1974), Rosen (1976) and Bruskewitz *et al.* (1981) described the results of dynamic prostheses. We now report our experience of implantable prostheses for stress incontinence in the male during the years 1973 to 1983 in the Urological Unit of the Royal Infirmary, Edinburgh.

Patients and Methods

Twenty-six male patients with disabling stress incontinence were either referred (22) or developed the condition following prostatectomy in our unit (4). The age range was 21 to 83 years, but if two young men aged 21 and 23 years respectively are excluded, the average age was 67 years. The aetiology of incontinence is shown in Table 1. The transvesical prostatectomy patients tended to appear earlier in the series, the incidence following TURP rising in the later period. One young man had a Y-V-plasty at 13 years of age, but the exact operative details are not available.

Table 1 Aetiology of Stress Incontinence

Following prostatectomy	
Transurethral	10
Transvesical	8
Retropubic	1
Sacral Nerve Injury	
Prolapsed lumbar disc	3
Abdominoperineal excision of rectum	1
Other	
Ruptured urethra secondary to fractured pelvis	2
Y-V-plasty to bladder neck	1

Three patients with retention due to a decentralised bladder, two following prolapsed lumbar intervertebral discs and one following abdominoperineal resection, became severely incontinent after TUR. All had failed to micturate despite the usual medical treatment. The two former patients had marked skeletal muscle weakness affecting the perineum and both lower limbs.

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The latter had no evidence of peripheral somatic nerve damage. One patient became incontinent following three operations on the lumbar spine. There was a marked deficit in both sphincter tone and perineal sensation. The bladder was atonic, but voiding was complete using manual suprapubic pressure.

Two patients showed severe stress incontinence following rupture of the urethra and pelvic fracture, one with intact bladder innervation and one with an atonic bladder trace and impotence.

The control of incontinence was by conventional means (Table 2). The interval between the onset of incontinence and operation is shown in Table 3.

Table 2 Control of Incontinence before Surgery

Plastic pants and pads	14
Catheter	9
Clamp	2
Uridome	1
Total	26

Table 3 Interval Between Onset of Incontinence and Operation

<3 months	*6 months*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*
2	3	7	7	1	1	5

Patients with an interval exceeding 60 months presented early in the series and were referred when the operation became available. Only two patients were operated upon within 3 months of the onset of incontinence and both had total incontinence. Figure 1 shows a voiding micturating cystourethrogram, the patient trying to interrupt the urinary flow with no evidence of sphincteric activity. Three were operated upon at 9 months, either because of severe incontinence showing no sign of improvement, or because of carcinoma of the prostate which had demonstrated hormonal response.

Pre-operative assessment

Only patients with stress incontinence were considered for surgery. Disabling stress-induced leakage was clinically demonstrable in all patients. Intravenous urography, cystourethroscopy, cystometry and urine cultures were carried out routinely. Videocystometry plus pressure studies were carried out only when there was doubt about the diagnosis. Urethral pressure profiles were not performed routinely in the face of obvious stress incontinence.

Peri-operative Treatment

Urinary tract infection was treated with the appropriate antibiotic. Large bowel preparation with oral kanamycin and metronidazole, plus mechanical clearance, was carried out. Twenty-four hours before surgery the perineum was shaved and neomycin ointment applied. Gentamycin, metronidazole and flucloxacillin were given for 5 days postoperatively, Septrin and metronidazole for 3 weeks thereafter.

Operative Technique—Kaufman III Prosthesis

All operations were performed through a midline perineal incision. The prosthesis was inserted as described by Kaufman (1973) with certain modifications. The device was placed as far anteriorly within the inferior pubic rami as could be comfortably arranged; the median raphe from bulb to perineal body was not dissected completely in an attempt to prevent posterior displacement. Bone staples as fixation points were introduced in 1977 (Fig. 2) following the late failure of two prostheses due to pulling-away of the crura from the bony arch.

Rosen Prosthesis

The Rosen prosthesis was inserted as described by Rosen (1976). Both wounds were closed with 3/0 subcutaneous Dexon or (more recently) Vicryl, with subcuticular skin closure by the same material.

Adjustment of Balloon Tension

Patients in the latter part of the series were operated upon under spinal anaesthesia and once the prosthesis had been installed, the bladder was filled and the patient asked to stress the bladder by coughing or lifting the shoulders off the table. The balloon tension was then adjusted by injection of Conray-280, a hypertonic solution, until the stress caused only minimal leakage. The patient was catheterised for 5 days and on bed rest for 3 to 5 days.

Results

Kaufman III Operation

Twenty-one patients had a Kaufman operation as a primary and one as a secondary procedure. The overall results as regards continence were assessed

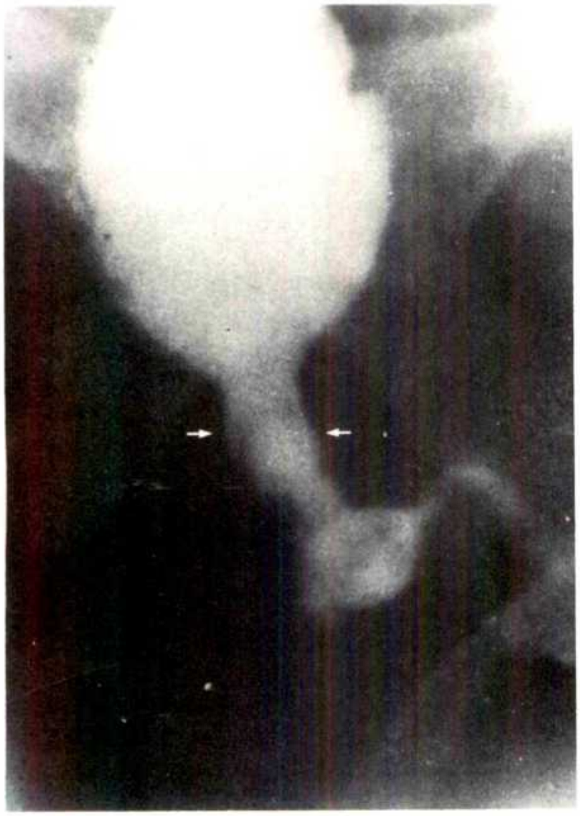

Fig. 1 Voiding micturating cystourethrogram (sphincter area marked by arrows).

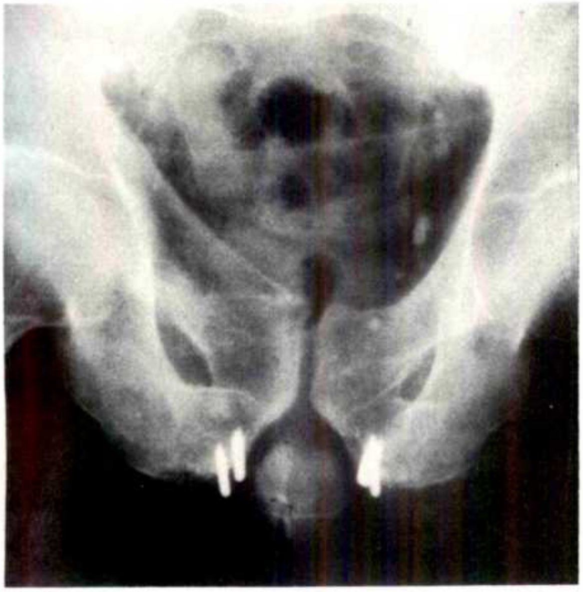

Fig. 2 Bone staples used as fixation points.

according to Kaufman (1973) (Table 4). The follow-up period is shown in Table 5 and the results in Table 6. Twelve patients have been assessed as cured, six much improved, and there have been four failures. The figures in brackets show those requiring re-operation to attain the state as shown. Within the successful group two patients required re-operation at 6 months and one at 2 years for recurrent incontinence. There were four failures. Two of these were immediate, one due to urethral necrosis and one to failure to attain compression of the urethra against a distorted pelvic diaphragm. Of the two late failures, one was due to retention in the face of an atonic lower motor neurone bladder and the other patient had two further operations at 2 and 3 years due to failure to maintain compression. This patient is 83 years old and the resulting loss of compression may be due to failure of the osteoporotic bone to hold staples and to loosening supports; at present he is again much improved following balloon augmentation.

Table 4 Assessment of Results (Kaufman Procedure)

- (*a*) Cured—no stress-induced leakage on severe stress.
- (*b*) Much improved—stress leakage of urine occurred under provocation, requiring the patient to wear either pads or tissues, but less than 4 per day with no protective clothing.
- (*c*) Failure—the patient required protective clothing (plastic pants) and more than 4 pads per day.

Table 5 Follow-up in 1983 (Kaufman Procedure)

< 1 year	*> 1 year*	*> 2 years*	*> 3 years*	*> 5 years*
1	3	7	4	7
		Total 22		

Table 6 Results (Kaufman Procedure)

Cured	12	(1)
Much improved	6	(2)
Failed	4	(2)
Total	22	

Patients requiring re-operation to attain status shown

Immediate Post-operative Complications

The immediate post-operative complications are listed in Table 7. The most severe was that of pressure necrosis of the urethra, which required a urethroplasty. In one patient a staple became displaced at 7 days, requiring immediate re-insertion. One patient developed a wound infection which settled on conservative treatment. Eight patients showed unacceptable incontinence post-operatively. This was treated by percutaneous injection of the balloon under image intensification and was successful in six cases. Two patients had unacceptable incontinence despite injection. The operation was repeated at 10 days, inserting a larger prosthesis with success in one patient; the other, a young man with fractured pelvis and severely disrupted arch, remains improved but still incontinent.

Table 7 Immediate Post-operative Complications (Kaufman Procedure)

Urethral necrosis	1
Displaced staple	1
Post-operative incontinence requiring balloon augmentation	8
Failure due to too small appliance, cured by insertion of larger prosthesis	1
Failure	2

Late Complications

Five patients became incontinent 6 months post-operatively or later, due either to loosening of supporting crura (2) or bone staples (3) (Table 8). Re-operation was successful in four of five cases. One patient has significant perineal pain, there being no obvious cause, but he refuses to have the prosthesis removed. One patient with incontinence due to repeated lumbar disc surgery and sphincter weakness, and who was shown to have an atonic bladder on cystometrography, developed retention at 6 months and was converted to a Rosen prosthesis. Three patients have required balloon augmentation 6 months, 6 months and 9 months post-operatively. There have been no cases of late infection.

Table 8 Late Complications (Kaufman Procedure)

Incontinence due to loose supports	5
Incontinence responding to balloon augmentation	3
Acute-on-chronic retention	1
Perineal pain	1

Rosen Prosthesis

Six patient had a Rosen prosthesis inserted as originally described (Rosen, 1976). The aetiology of incontinence is shown in Table 9. Four had this carried out as a primary procedure and two following failure of a Kaufman prosthesis. The pre-operative and post-operative care was as for the latter procedure.

Table 9 Aetiology of Incontinence

Primary Rosen	
Following prostatectomy	
transurethral	2
transvesical	2
Secondary Rosen	
Neurogenic incontinence, decentralised bladder and retention post-Kaufman	1
Transvesical prostatectomy. Failed Kaufman, secondary urethral necrosis	1
Total	6

Immediate Post-operative Complications

One patient developed a urethral fistula (Table 10). There were no other immediate post-operative problems.

Table 10 Post-operative Complications (Rosen Procedure)

Post-Operative Complications	
Immediate	
Urethral necrosis	1
Late	
Revision of reservoir function	2
Urethral fistula	5

Follow-up to Fistula Formation

1 year	*1 year*	*2 years*	*4 years*	*Total*
2	1	2	1	6

Long-term Complications

The five remaining patients developed fistulae at intervals ranging from 6 months to 5 years (Table 10). Two patients required revision due to failure of hydraulics. All commented on the discomfort of manipulating the balloon reservoir. All prostheses have now been removed. The follow-up period to fistula formation is shown in Table 10. An acceptable degree of continence was achieved in the five patients until the development of fistulae.

Discussion

Stress incontinence in the male usually follows a well-defined event, the most common being prostatectomy for primary prostatic disease, the patient having normal bladder innervation. Incontinence may follow TURP where retention is secondary to major sacral nerve damage, as in the case of prolapsed lumbar intervertebral disc. Pre-operative evaluation by visual demonstration of stress, together with bladder pressure studies, was used to select only those patients with pure stress incontinence for surgery. Patients with severe urge and urge incontinence demonstrated by combined videocystometry and cystometrography were treated medically and not considered for a prosthetic implant, the majority being elderly with evidence of impaired cortical control, although Reid *et al.* (1980) reported some success with a similar group.

The Kaufman III procedure has proved to be an operation with little morbidity, no mortality and reproducible results. The overall success rate of 16 of 22 patients (73%), with a follow-up period of 3 months to 10 years, compares with Kaufman's earlier results of 76% and the 65% reported by Reid *et al.* (1980) over a rather shorter follow-up period. The prosthesis is in itself inert, producing little in the way of inflammation or local pain. Fixation of the restraining straps by means of the corpora (Kaufman) or by bone staples, despite sewing in the latter to the fascia and periosteum, has not abolished recurring incontinence due to loosening of the prosthesis. The use of mechanical (staple) fixation does allow the operation to be repeated should failure occur. This method gives a transverse lie to the straps with little or no inward pull and thus less urethral compression in patients with a deep ischiopubic arch. Continence is then dependent upon a greater volume of fluid being injected into the balloon and may be difficult to attain. Urethral erosion occurred in 1 of 22 patients due to over-filling of the balloon at operation. Judging the exact balloon tension is difficult, despite the use of urethral pressure profilometry, the latter not really being a guide to post-operative continence. It is a theoretical advantage to have as few post-operative percutaneous injections as possible, thus reducing the risk of sepsis, though this has not been a problem. The use of spinal anaesthesia, which allows the patient to test the prosthesis intra-operatively, has helped with balloon adjustment. The intra-operative stress test demonstrated two patients with ineffectual prostheses, and their operations were immediately repeated successfully. Eight patients required a degree of balloon augmentation post-operatively with a good result in six. All had hypertonic fluid injection. This may explain the discrepancy between the results of injection in our patients and those reported by Kaufman. Of eight patients who relapsed later than 6 months post-operatively, seven were returned to a satisfactory status, three by injection and four by re-operation.

Five patients had incontinence with decentralised, poorly contractile bladders. The aetiology in three patients was nerve compression secondary to a prolapsed lumbar intervertebral disc; one followed an abdominoperineal resection and one a fracture of the pelvis with urethral disruption and nerve damage. Three of five patients had TUR-induced incontinence following retention due to the above condition, and to the standard investigations has now been added sphincter electromyography to detect this latter high-risk group. The first patient with a lower motor neurone bladder developed retention 6 months post-operatively and had the Kaufman prosthesis removed; subsequently the other three, with more careful adjustment of the balloon tension, have been able to void satisfactorily and have been continent.

There were five cases of invasive prostatic carcinoma (T3 − 4 M+) showing good hormonal response but with severe stress incontinence. All were treated by either Rosen or Kaufman prostheses; they have been followed for 1 to 5 years and the insertion of prostheses does not seem to have adversely affected their disease.

The Rosen prosthesis is simple to install and operate but unfortunately in our hands has eventually given rise to fistulae in all patients and is now no longer used.

Recently the AS791/792 artificial sphincter has been shown to be both effective and to have a low complication rate (Stephenson *et al.*, 1983) within a short follow-up period. It has been successful in both post-prostatectomy patients and, more importantly, in patients with complex neurologically-induced urinary incontinence.

Stress incontinence in the male due to a damaged sphincteric mechanism may now be treated by the Kaufman III prosthesis with a success rate exceeding 70%. It was also successful in controlling incontinence in three of five patients with neurologically-induced sphincter weakness and decentralised bladders. A dynamic prosthesis offers a greater degree of volitional control, but the elderly patient may have neither the cortical control nor the manual dexterity to make use of it. It is more costly and also prone to a higher complication rate, though this may not be applicable to the new sphincter (AS791/792). In the light of this and other series, treatment with the Kaufman III prosthesis appears to be the procedure of choice for uncomplicated stress incontinence following prostatectomy.

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The Authors

J. W. Fowler, FRCSE, Consultant Urologist.
C. D. Auld, MD, FRCSE, Urological Registrar.

Requests for reprints to: J. W. Fowler, Department of Urolog
Royal Infirmary, Edinburgh EH3 9YW.

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The Undescended Testis in Adult Life

T. F. FORD, M. CONSTANCE PARKINSON and J. P. PRYOR

St Peter's Hospitals and Institute of Urology, London

Summary—The management of the undescended testis in the adult patient presents problems in terms of locating the impalpable gonad, the risk of malignancy and prognosis with regard to fertility. CT scanning has been used to locate four intra-abdominal testes. The risk of malignancy has been assessed by determining the incidence of carcinoma *in situ* after orchiectomy or testicular biopsy in 90 patients (112 testes). Carcinoma *in situ* was found in 4 of 16 abdominal, 3 of 44 inguinal and none of 52 scrotal testes following orchiopexy in childhood. Seventy per cent of undescended testes in adult patients had no evidence of spermatogenesis. This fact, together with the risk of malignancy in those testes in which germ cells are present, suggests that orchiectomy should be performed in unilateral cases. Testicular biopsy is essential if an undescended testis is to be preserved for androgenic function.

The incidence of testicular maldescent in infants at the age of 1 year is approximately 0.8% (Scorer, 1964) and in adults approximately 0.3% (Campbell, 1959). The difference presumably reflects treatment or late spontaneous descent. This cryptorchid population, consisting of both treated and untreated patients, may present in adult life and in order to assess the therapeutic options it is necessary to consider the location of the testis, its spermatogenic potential, the risk of malignancy and the need to preserve androgenic function. The present study was undertaken in an attempt to review these various aspects.

Patients and Methods

In the period 1964 to 1984, 90 post-pubertal patients (all except one aged 16 or over) with a history of unilateral or bilateral testicular maldescent were seen in the St Peter's Hospitals. Sixty-five presented with infertility, seven with testicular pain, 3 with impalpable gonads, 10 with ectopic, palpable testes and 5 with somatosexual ambiguity. Histological material, in the form of orchiectomy specimens or testicular biopsies, was available from 112 maldescended and 30 contralateral, normally descended testes. At the time of tissue sampling, 60 of the maldescended testes were still in an ectopic position while 52 were located in the scrotum, the patients having undergone a successful orchiopexy 5 to 23 years previously. All histological material has been reappraised and the hospital records reviewed.

The risk of germ cell tumour formation has been retrospectively assessed by determining the incidence of carcinoma *in situ* (CIS) in these testes. The criteria for the diagnosis of CIS have been reported previously (Pryor *et al.*, 1983). Spermatogenesis was assessed in testicular biopsies using the Johnsen score count (Johnsen, 1970) and by recording the number of testes in which no germ cells were demonstrable histologically (Sertoli cells only syndrome). In those patients who had had a successful orchiopexy in childhood, the age at which the operation was performed was noted.

In five further patients, computed axial tomography (CT scanning) was used in an attempt to locate the site of an impalpable testis.

Results

CT scanning successfully located the unilaterally impalpable testes on each of the four occasions on

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Table 1 Clinical and Pathological Findings in Patients with Testicular Carcinoma *in situ*

Patient (Age)	*Indication for surgery*	*Testis with CIS*	*Contralateral testis*	*Comment*
S.R. (25)	Infertility	Abdominal MJS = 1.3. Orchiopexy	Abdominal. CIS. Orchiectomy	Lost to follow-up
J.M. (17)	Intra-abdominal "testes"	Abdominal ovotestis. Gonadectomy	Abdominal ovotestis. CIS + gonadoblastoma. Gonadectomy	46XX true hermaphrodite
E.S. (35)	Infertility	Inguinal. Orchiectomy	Normal	Alive and well for 20 years
P.C. (22)	Pain	Inguinal. MJS = 3.6. Orchiopexy	Normal	Ghost seminoma 5 years later
L.F. (14)	Risk of malignancy	Inguinal. Orchiectomy	Streak	46XY/45XO Gonadal dysgenesis
A.H. (28)	Infertility	Scrotal. MJS = 3.0	Inguinal Orchiectomy 10 years previously	Diagnosed 1984

MJS = mean Johnsen score.

Table 2 Incidence of Carcinoma *in situ* in Relation to Location of the Testis

	Histological material					
Location	*Orchiectomy*	*Biopsy*	*Total*	*Number with SCO*	*Range of MJS*	*CIS*
Abdominal	10	6	16	10	1.8-2.2	4
Inguinal	21	23	44	32	1.0-3.8	3
Scrotal (previous successful orchiopexy)	1	51	52	12	1.6-8.7	0
Scrotal (contralateral normally descended)	0	30	30	6	1.0-9.5	1

MJS = mean Johnsen score. SCO = Sertoli cells only. CIS = carcinoma *in situ*.

which it was used, and confirmed unilateral testicular agenesis in another patient.

The typical histological appearances of carcinoma *in situ* were found in 8 testes from 6 patients (Table 1). In addition, one further intra-abdominal testis showed the borderline appearances of severe atypia (Pryor *et al.*, 1983). One patient (Case 2) had been wrongly diagnosed as a 46XX male in childhood and underwent a laparotomy to assess his presumptive intra-abdominal testes. Both proved to be ovotestes containing CIS in the testicular portion and, in one, a focus of gonadoblastoma. The diagnosis of CIS was made on testicular biopsy in three patients, one of whom has been lost to follow-up (Case 1) and in one other it was noted in a biopsy of a solitary testis in March 1984, so that only a very brief period of follow-up is available (Case 6). The remaining patient (Case 4) had a testicular biopsy performed at the time of orchiopexy for a painful inguinal testis. Five years later, the then high scrotal but still painful testis was excised. Histological examination showed areas of necrosis consistent with a "ghost" seminoma.

Table 3 Mean Johnsen Scores in Scrotal Testes and Age at Orchiopexy

Age at orchiopexy (years)	*Number*	*Mean Johnsen score*	
		Range	*Median*
4-8	13	2.0-8.6	6.9
9-12	19	2.0-8.2	2.7
13-16	13	1.6-8.7	2.4

Histological assessment of spermatogenesis in 6 abdominal and 23 inguinal testes that were biopsied at the time of orchiopexy showed mean Johnsen scores ranging from 1.8 to 2.2 and 1.0 to 3.8 respectively (Table 2). Of the total of 60 persistently undescended testes, 42 (70%) showed no evidence of germ cell formation (Sertoli cells only). In those testes that had been brought down in childhood, there appeared to be a correlation between the age at which orchiopexy was performed and the subsequent mean Johnsen scores on later biopsy (Table 3).

The incidence of CIS in relation to the position of the gonads is shown in Table 2. The absence of histologically demonstrable germ cells (Sertoli cells only) precludes the risk of germ cell tumour formation; thus, 4 of the 6 abdominal and 3 of the 12 inguinal testes at risk contained elements of carcinoma *in situ*. CIS was not identified in any testis that had been successfully brought down in childhood but in one of 30 contralateral, normally descended testes in patients with unilateral maldescent.

Discussion

Established methods of locating impalpable testes such as retrograde venography (Khan *et al.*, 1982), selective arteriography (Khademi *et al.*, 1980) and laparoscopy (Scott, 1984) are invasive and necessarily carry a risk of morbidity. The success of CT scanning reported here would confirm that of other workers (Lee and Glazer, 1982) and it must be regarded as the method of choice for pre-operative localisation.

Spermatogenesis was severely impaired in all persistently undescended testes in this study, although allowance must be made for the fact that many of the patients presented with infertility. Certainly, the contribution of such testes to the production of spermatozoa is minimal and there can be little justification for preserving such a testis on those grounds.

The natural history of testicular carcinoma *in situ* has yet to be fully elucidated. Of 24 cases in the world literature in which the diagnoses were made on testicular biopsies, 14 have subsequently developed invasive germ cell tumours over periods of up to 9 years, although follow-up is incomplete (Sigg and Hedinger, 1981; Skakkebaek *et al.*, 1981; Pryor *et al.*, 1983). An actuarial projection based on 23 reported cases suggested an incidence of invasive tumour growth of 75% at 7 years (Skakkebaek *et al.*, 1982). Clearly, a close association with invasive tumours does exist, but whether it is enough to justify immediate excision of a solitary testis is debatable. A policy of close surveillance (including repeat biopsies) may be warranted since, if an invasive tumour develops, orchiectomy alone is curative in 80% of stage I non-seminomas (Peckham *et al.*, 1983).

The incidence of carcinoma *in situ* in unselected groups of patients with a history of maldescent similarly remains unclear. Krabbe *et al.* (1979) reported that 4 of 50 men (8%) previously treated for undescended testes had CIS on subsequent testicular biopsy. In the present study, none of the 50 men whose testes had been brought down into the scrotum had evidence of CIS. However, the two groups are not strictly comparable since almost all men in the present series had presented with infertility, whereas in the Danish study the group was apparently unselected except in their agreement to undergo testicular biopsy. In addition, other factors may be operative since the incidence of germ cell tumours is higher in Denmark than in the United Kingdom. The incidence of CIS in the present report may have been skewed by the inclusion of two patients with somatoasexual ambiguity. However, true hermaphrodites are not at excessive risk of testicular tumours (Van Niekerk, 1976), although there is an increased risk of gonadoblastomas in gonadal dysgenesis (Scully, 1970). Carcinoma *in situ* has not been reported previously in such patients and its incidence in patients with somatoasexual ambiguity in general is unknown (Skakkebaek *et al.*, 1982).

Certain conclusions can be drawn with regard to the management of the undescended testis in the adult patient. It is clear that the higher a testis is arrested in the course of its descent, the greater is the incidence of carcinoma *in situ*. This, together with the lack of spermatogenic potential, warrants orchiectomy in unilateral cases. If a testis is to be preserved for androgenic function, then a biopsy is essential to exclude carcinoma *in situ*.

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The Authors

T. F. Ford, MA, DM, MCh, FRCS, Senior Registrar in Urology, St Peter's Hospitals.

M. Constance Parkinson, BSc, MD, MRCPath, Consultant Histopathologist, St Peter's Hospitals and Institute o Urology.

J. P. Pryor, MS, FRCS, Consultant Urologist, St Peter's Hospitals.

Requests for reprints to: T. F. Ford, St Paul's Hospital, Endell Street, London WC2H 9AE.

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A Comparison Between Ultrasonography and Laparoscopy in Localising the Impalpable Undescended Testis

P. S. MALONE and E. J. GUINEY

Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Irish Republic

Summary—In 11 boys, 3 of whom had bilateral and 8 unilateral impalpable testes, ultrasonography was used to identify the location of the testes. The results of ultrasonography are compared with those of laparoscopy in the same patients.

The testes were absent in two instances. The remaining 12 testes were accurately located by laparoscopy. Ultrasonography demonstrated the testes in only two cases.

Impalpable undescended testes pose a significant clinical problem. Accurate pre-operative localisation is of considerable value, particularly with the increasing use of microsurgical transplantation. Of the many methods used laparoscopy has recently increased in popularity and is now regarded as a safe and effective technique (Madrazo *et al.*, 1979; Scott, 1982; Malone and Guiney, 1984). It is an invasive procedure requiring general anaesthesia and this has prompted us to study ultrasonography in localising impalpable testes. We present a small series comparing the effectiveness of laparoscopy with ultrasonography.

Patients and Methods

There were 11 patients with ages ranging from 3 to 12 years and a mean age of 6 years. Three patients had bilateral and eight had unilateral impalpable testes. We were seeking to demonstrate 14 testes.

Each patient had an ultrasound examination of the scrotum, inguinal canal, pelvis and abdominal cavity. Without knowing the ultrasound results, laparoscopy was performed using the method we have previously described (Malone and Guiney, 1984). All patients subsequently had surgical explorations confirming the sites of the testes.

Results

Our findings are classified in the Table.

Laparoscopy accurately located the 12 testes which were present. In one case a blind-ending vas deferens associated with hypoplastic testicular vessels was seen and we correctly predicted that the testis was absent. In the last case the vas and testicular vessels were seen passing through the internal inguinal ring but during exploration of the inguinal canal an atrophic testis was found and excised.

Ultrasonography demonstrated a testis in only two cases. One was abdominal, lying 4 cm from the internal ring, and the other was canalicular. Exploration confirmed the accuracy of these locations. In the remaining cases ultrasonography was of no benefit. There were no false positive results.

Successful orchiopexy was performed on 9 of the 12 testes present. In the remaining three cases

Table Sites of the 14 Testes

Site	*Number*
Abdominal	7
Just canalicular	2
Canalicular	3
Absent/atrophic	2
Total	14

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surgery was deferred because the testes were too high for standard orchiopexy techniques to be successful. In our view, accurate localisation greatly facilitated the surgeon in his approach and in assessing the likelihood of a successful outcome.

Discussion

Ultrasonography is commonly used in investigating urinary tract abnormalities (Sanders, 1975). Madrazo *et al.* (1979) described its use in demonstrating impalpable undescended testes. They accurately located eight of the nine canalicular testes but they could not identify those lying in the abdominal cavity. The overlying gas-filled bowel interfered with the examination and this, associated with the small size of the testis, made demonstration impossible.

In this small series only three testes were canalicular and ultrasonography identified one of them. We did successfully locate one abdominal testis. In the remaining cases ultrasonography did not help in any way. In our previous report (Malone and Guiney, 1984) there were 45 impalpable tests, 13 of which were canalicular. According to Madrazo's study, ultrasonography would not have helped in the remaining 32 cases and our figures in this study support that view.

In contrast, all 12 testes present were accurately located with laparoscopy and the absence of one testis was also correctly predicted. In this series there were only three canalicular testes present and this small number is insufficient to assess the accuracy of ultrasonography in demonstrating a testis at this site. Further study is obviously needed. There is no doubt that laparoscopy is superior in localising abdominal testes.

We would, therefore, recommend laparoscopy as the simplest and most effective technique for localising impalpable testes. However, a preoperative ultrasound examination of the inguinal canal may demonstrate the testis if it is in the inguinal canal and thus spare the patient an invasive procedure.

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The Authors

P. S. Malone, FRCSI, Surgical Research Fellow, King's College Hospital, London.

E. J. Guiney, MCh, FRCS, FRCSI, Director of Research, Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin.

Requests for reprints to: E. J. Guiney, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Irish Republic.

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Is the Scrotal Testis Normal in Unilateral Cryptorchidism?

R. S. KIRBY, C. R. CHAPPLE, SHIRLEY P. WARD and C. WILLIAMS

Department of Urology, Middlesex Hospital, London; Department of Surgery, Royal Hospital, Wolverhampton

Summary—Bilateral testicular biopsies were performed on 66 children undergoing orchiopexy for unilateral cryptorchidism and the tubular fertility index (TFI) recorded. The results in both the descended and undescended testes at various ages were compared with previously reported control data. There were no significant differences between the germ cell activity of the scrotal testis in cases with unilateral cryptorchidism and that of controls. By contrast, the mean TFI of the undescended testis was significantly less than that of control patients of all ages. In neither group was there evidence of a progressive loss of germ cell activity during childhood. It is concluded that there is little to be gained from very early orchiopexy, performed before the third year of life.

It is widely accepted that in patients with unilateral cryptorchidism, the undescended testis may suffer impaired germ cell function. However, there is controversy as to the fertility of the scrotal testis in these patients: while Farrington (1969) has reported compensatory hypertrophy, Mengel *et al.* (1974) have claimed that a progressive reduction in germ cell activity occurs.

In order to establish whether either of these assertions is correct we performed bilateral testicular biopsies on 66 children with unilateral cryptorchidism and determined the tubular fertility index for each testis. The results are compared with those obtained from a previously reported group of 79 control patients (Farrington, 1969) with normally situated testes.

Patients and Methods

Sixty-six children with a mean age of 8.2 years

Table Tubular Fertility Index in Controls and Patients with Unilateral Cryptorchidism

	Age (yrs)	*Mean tubular fertility index*	*Standard error*	*No. of cases*	*Statistical significance*
Controls	0-3	63.8	± 2.0	54	
	4-7	85.9	± 2.6	12	
	8-14	82.1	± 6.7	13	
Scrotal testis (in cases of unilateral maldescent)	0-3	76.4	± 6.3	5	NS
	4-7	81.8	± 5.7	19	NS
	8-14	89.1	± 3.8	26	NS
Undescended testis (in cases of unilateral maldescent)	0-3	11.0	± 6.3	6	$P < 0.05$
	4-7	52.9	± 7.7	26	$P < 0.05$
	8-14	45.1	± 6.7	34	$P \leqslant 0.05$

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

(± 8.2 SD) who presented with unilateral cryptorchidism underwent bilateral testicular biopsy at the time of orchiopexy. Control data were derived from previously published results of testicular biopsies in 79 patients with normally situated testes and a mean age of 3.5 years (± 3.9 SD) (Farrington, 1969).

Operative biopsy specimens were fixed in Bouin's fluid, set in paraffin wax and sectioned at a thickness of 6 microns. In each histological specimen the number of tubules containing spermatogonia were counted (Figs 1 and 2) and the results expressed as a value per 100 tubules (TFI) (Mack *et al.*, 1961). Statistical analysis of the results was performed using Students' *t* test and the level of significance was taken as 5%.

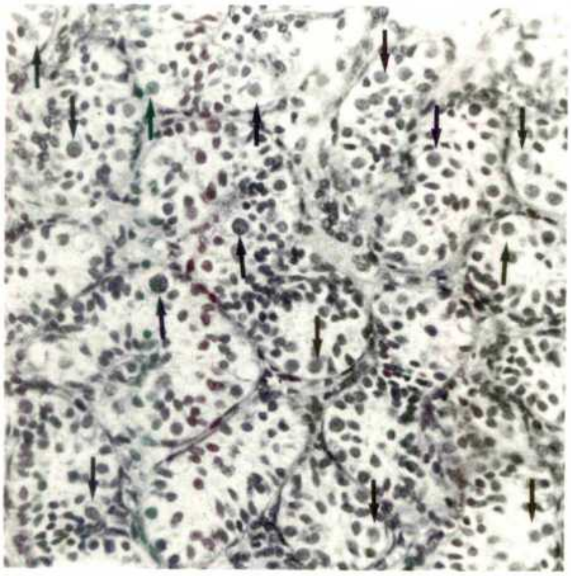

Fig. 1 Section of a descended testis with a normal TFI. The majority of tubules contain spermatogonia (arrows) (H and E × 487).

Results

The results are summarised in the Table and in Figures 3 to 5. The mean TFI of the scrotal testis did not differ significantly from that of controls. By contrast, the mean TFI of the undescended testes was significantly lower than that of controls at all ages, although there was no evidence of a progressive reduction of germ cell activity during childhood.

Discussion

The results of this study appear to cast doubt upon the contention by Mengel *et al.* (1974) that, in patients with unilateral cryptorchidism, the germ cell function of the descended testis may in some way be damaged by the presence of an undescended organ. Nor is the contrary hypothesis of Farrington (1969), that the descended testis undergoes germ cell hypertrophy to "compensate for the deficiency observed in the undescended testis", borne out by our data. Instead our studies reveal that, at least in terms of TFI, the germ cell activity

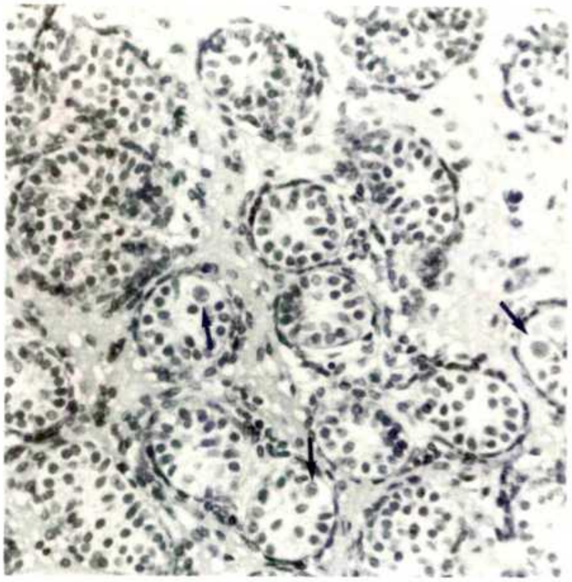

Fig. 2 Section of an undescended testis with a low TFI. Very few of the tubules contain spermatogonia (arrows) (H and E × 487).

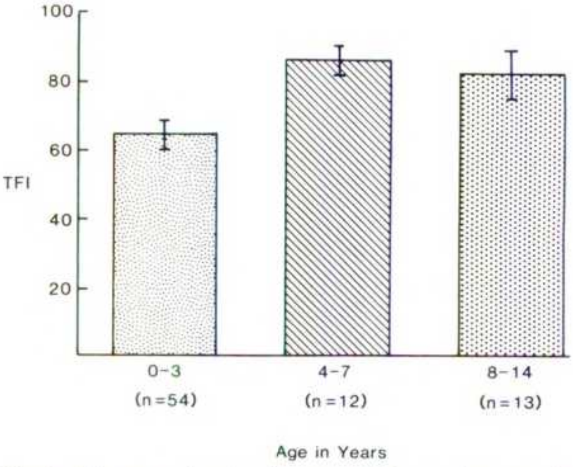

Fig. 3 Histogram showing the mean TFI at various ages in controls (data from Farrington, 1969).

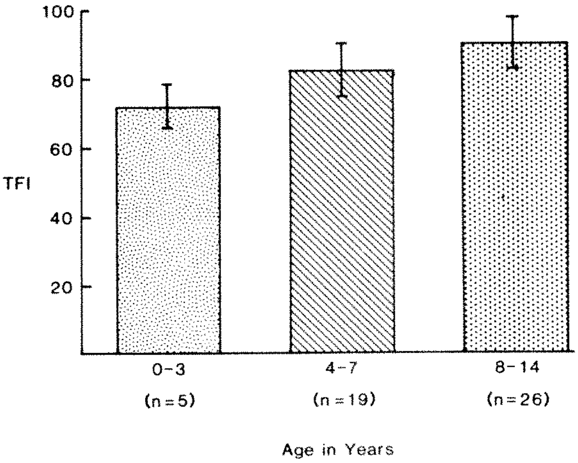

Fig. 4 Histogram showing the mean TFI of the scrotal testis in children with unilateral cryptorchidism at various ages.

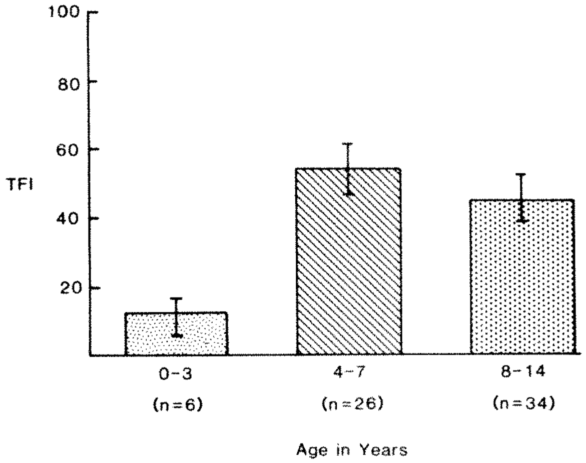

Fig. 5 Histogram showing the mean TFI of the undescended testis in children with unilateral cryptorchidism at various ages.

of the descended testis in patients with unilateral cryptorchidism is normal throughout childhood.

By contrast, the mean TFI of the undescended testis is significantly lower than that of the normal gonad at all stages. The observation that germinal cell deficiency is present from birth, and that there is no evidence of a progressive loss of germ cells, suggests that the deficiency may be congenital in origin rather than the result of hyperthermia-induced damage to germinal epithelium (Moore and Oslund, 1924).

It is concluded that, psychological and cosmetic indications apart, there is little to be gained from very early orchiopexy, which some authors (Mengel *et al.*, 1974) have suggested should be performed before the third year of life.

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The Authors

R. S. Kirby, FRCS, Senior Registrar in Urology, Middlesex Hospital, London.
C. R. Chapple, MB, BS, Registrar in Surgery, Selly Oak Hospital, Birmingham.
Shirley P. Ward, MRCPath, Consultant Pathologist, Royal Hospital, Wolverhampton.
C. Williams, FRCS, Consultant Surgeon, Royal Hospital, Wolverhampton.

Requests for reprints to: R. S. Kirby, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

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Familial Torsion of the Testicle

J. O. R. STEWART and A. K. MAITI

Department of Surgery, County Hospital, Lincoln

Summary—Two families in which several siblings suffered torsion of the testicle are described. The literature is reviewed and comments made on management.

Torsion of the testicle in siblings is rarely reported. Two families in which three out of four and two out of four siblings developed torsion are described and illustrate once more the importance of early diagnosis, urgent treatment and immediate contralateral fixation. No predisposing anatomical abnormalities were found in the contralateral testicle or in other members of the families available for examination.

Patients

Family A

1. R.H., aged 17 years, was admitted with a 4-h history of a painful right testicle since waking. He had a previous history of left torsion 2 months earlier, when the testicle proved to be viable and was fixed with sutures. There was subsequent wound infection which still persisted. Examination showed oedematous right scrotal skin with a very tender, normal-sized right testicle. A diagnosis of torsion was made and exploration showed an intravaginal twist of a viable testicle. It was fixed with catgut sutures and the scrotum drained.
2. D.H., aged 17 years, was admitted with a history of waking with a painful right testicle. Examination showed a swollen, tender scrotum and right testicle with transillumination. At operation a diagnosis of torsion of the testicle was confirmed with an intravaginal, anticlockwise twist. Untwisting showed a viable testicle which was fixed, together with the left side.
3. J.H., aged 28 years woke up with severe right testicular pain. Examination showed a lax hydrocele surrounding a tender, normal-sized testicle. At operation the testicle was twisted, congested and blue. It was untwisted and found to be viable, so was fixed with linen sutures together with the left side.

Family B

4. V.W., aged 15 years, was admitted with a history of a painful left testicle for 4 days. Examination showed a red, tender scrotum. A diagnosis of torsion was made clinically. Exploration through a midline scrotal incision showed a three and a half turn torsion of the cord with a gangrenous testicle. Orchiectomy was performed with drainage. The right testicle was fixed with linen sutures.
   Three years later he was admitted urgently with a painful right testicle of 4 h duration. Examination showed a red scrotum and a swollen, tender testicle. A diagnosis of torsion was made and operation performed (in spite of previous fixation). A red, swollen epididymis and spermatic cord were found. The vascularity of the testicle was not impaired, so it was fixed again and a course of Magnapen given in view of the presumed diagnosis of epididymo-orchitis.
5. K.W., aged 21 years, was admitted urgently with a 4-h history of right scrotal pain since waking. Examination revealed a very tender right testicle. A diagnosis of torsion was confirmed by exploration. The testicle was viable on untwisting. It was fixed with linen sutures, as was the left side, through a separate scrotal incision.

Discussion

The present observations were made when the fourth and remaining member of family A presented in the Out-patient Clinic with the unusual request that his testicle might be fixed as he did not want to suffer the fate of his three brothers, all of whom had "had operations for twisted testicles". Investigation confirmed his statement and when

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another patient (K.W.) told us that his brother had had a torsion, a search of the literature was carried out and confirmed the rarity of the occurrence. Only three cases of familial torsion have been reported (Cunningham, 1960; Castilla *et al.*, 1974; Picard, 1975). This is surprising in that torsion is common and since all of the predisposing anatomical abnormalities are well recognised it would seem reasonable to assume that their genetic basis might be present in more than one member of a large family. This aspect has been considered by Castilla *et al.* (1974), who postulated an "autosomal or X-linked recessive pattern of inheritance" for the abnormality.

Cunningham (1960) examined six other members of a family (three of whom suffered torsion) and claimed all had abnormal hypermobility, but no criteria for this test were described and it would seem that features such as scrotal laxity and ambient temperature might well influence mobility. In addition, it is the intravaginal mobility that is relevant and this can hardly be assessed. We have not found any remarkable abnormality in three siblings or parents of the above families. In addition, the unaffected testicles of the patients showed no abnormalities. Neither family had a previous family history of torsion.

Commonly described diagnostic features noted in this study included the onset of pain on waking (four cases) and transilluminant hydroceles. The latter feature led Cunningham (1960) to suggest aspiration as a diagnostic measure and he based his management—manual or operative untwisting—on the degree of blood staining.

The previously pronounced axioms in this condition are confirmed, *i.e.* early operation is mandatory for a painful testicle in the under-25 age group in spite of recent advances in diagnosis such as ultrasound, radioisotope scanning and Doppler studies of vessels, which may only lead to procrastination (King and Whelan, 1984). It saved five testicles out of six in this series.

The other testicle should be fixed immediately since early recurrence is a real hazard (Case 1) (Picard, 1975), and patients may not wish to return for a second operation (Cunningham, 1960).

On the basis of Case 4 it may be assumed that previous fixation is likely to have been successful and that a diagnosis of epididymo-orchitis and postponed intervention is more tenable under these circumstances.

The answer to the more philosophical question of what policy should be adopted for the other members of these families, as raised by the request from the remaining brother in Family A, is not quite so clear, although in his case it was simplified by his plea for surgery. To suggest a surgical operation, albeit a minor one, with possible morbidity (Case 1) to a healthy young man on the basis of a few published reports, is hardly acceptable. It would therefore seem more reasonable to warn the siblings of the dangers and the need for immediate attendance, direct to the hospital if necessary, if there is sudden onset of scrotal pain, especially on waking. This conforms with the policy suggested by Cunningham (1960) in the case of siblings with "excessive mobility". However, where there was a history of previous pain in the testicle, he advocated "fixation of one or both testicles". We have not encountered this situation but it appears to be a definite indication for offering prophylactic bilateral orchiopexy rather than the strict cautionary advice recommended above.

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The Authors

J. O. R. Stewart, FRCS, Consultant Surgeon.
A. K. Maiti, FRCSE, Surgical Registrar.

Requests for reprints to: J. O. R. Stewart, Department of Surgery, County Hospital, Sewell Road, Lincoln LN2 5QY.

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Treatment of Hydrocele of the Testis with Aspiration and Injection of Tetracycline

A. BØDKER, W. SOMMER, J. T. ANDERSEN and J. K. KRISTENSEN

Department of Surgery D, Section of Urology, Rigshospitalet, Copenhagen, Denmark

Summary—Ten males over the age of 60 with primary hydrocele of the testis were treated by aspiration and injection of tetracycline. Nine were cured and one patient had a small recurrence but was satisfied with the result. There were no cases of haematoma or infection. We recommend this method since it can be carried out as an out-patient procedure with minimal side effects and at low cost.

Tetracycline is commonly used as a sclerosing agent in controlling malignant pleural effusions (Rubinson and Bolooki, 1972) and has lately been described as useful in the treatment of hydrocele of the testis (Kaye, 1982). Being both antibacterial and sclerosing, tetracycline seems to be an ideal agent in this context. We report the results of a prospective study using aspiration and tetracycline instillation for sclerotherapy of the hydrocele.

Patients and Methods

Ten males, median age 72 years (range 63-89), entered the trial. All had a unilateral primary hydrocele with no sign of hernia or other scrotal disease. None of the patients was allergic to tetracycline. The hydrocele had been present for a median period of 1 year (range 5 weeks-6 years). One patient had been treated several times by simple aspiration and another had a recurrent hydrocele 5 weeks after surgical treatment.

The median volume of fluid aspirated from the hydrocele was 180 ml (range 22-400 ml). In nine cases the aspirated fluid was clear and straw-coloured. The patient with a recurrent hydrocele following surgical treatment had a blood-stained tap.

The scrotal wall overlying the most cranial part of the hydrocele was infiltrated with lignocaine 1% and the hydrocele was punctured with a 17 gauge needle. The stylet was removed and the fluid evacuated through the plastic sheath left in the hydrocele sac; 500 mg of tetracycline diluted in 5 ml isotonic saline were then injected and the plastic sheath removed. The patients were treated on an out-patient basis and discharged after 1 hour's observation. All patients were seen 2, 6, 12 weeks and 6 months after treatment.

Our protocol required that recurrence of the hydrocele after two injections should be followed by surgical treatment.

Results

Nine of the 10 patients were cured of their hydrocele. Five had only one instillation. Two patients developed a recurrent hydrocele on the same side 2 weeks after the primary treatment and a further two after 3 and 5 months. The procedure was repeated in these four patients and there was no sign of recurrence during the following 6 months.

No significant difference was found in the size of the hydroceles between the patients treated once and those treated twice.

One patient from whom 375 ml of fluid were aspirated had a small recurrence, but he was satisfied with the result. He refused a second injection and the hydrocele did not increase in size during the follow-up period. Two patients experienced scrotal pain immediately after the injection and

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were given a spermatic cord block with lignocaine 1% at the superficial inguinal ring with subsequent relief of pain. All other treatments were uneventful and no haematomas or infections were seen.

Discussion

The standard treatment of hydrocele is surgical and this is widely accepted as the most effective (Stewart, 1979). The disadvantage of surgical treatment is a high incidence of complications such as haematomas and infection (Moloney, 1975). Although these can be minimised with careful surgery (Lord, 1964), post-operative scrotal haematomas still occur quite frequently. Simple aspiration as the only treatment for hydrocele is considered a helpful palliative method in poor-risk patients, but rarely leads to cure (Stewart, 1979). Aspiration followed by injection of sclerosing solutions has been known for centuries (Landes and Leonhardt, 1967). In a recent trial using a 3% solution of sodium tetradecyl sulphate, 10 of 20 patients were cured after one injection, while the remainder had up to three treatments (average number of injections 2-6) (Macfarlane, 1983). The use of a 2.5% solution of phenol in water has also been advocated, although it seems that repeated injections are required with this agent, especially in the large hydroceles (Nash, 1979).

We have chosen tetracycline because it is antibacterial, sclerosing and cheap. Its efficiency as a sclerosant is related to the extremely low pH of tetracycline in solution (ranging from 2.0 to 3.5, depending upon the quantity and composition of the diluent) (Rubinson and Bolooki, 1972). The scrotal pain that developed in two patients was possibly due to local irritation resulting from the low pH of the solution. In two of the patients with recurrence, repeat procedures were performed only 2 weeks after the initial injection. It is possible that these patients should have been observed for a longer period of time, because re-accumulated fluid due to the local irritative effects of the sclerosant slowly disappears over 3 to 4 weeks (Macfarlane, 1983).

Although this small study permits only limited conclusions, the advantages of sclerotherapy with tetracycline are evident. The patient can be treated on an out-patient basis, side effects are minimal and expense is low. We conclude that treatment of hydrocele of the testis with aspiration and injection of tetracycline is a useful alternative to surgery in elderly males.

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The Authors

A. Bødker, MD, Registrar.
W. Sommer, MD, Registrar.
J. T. Andersen, MD, PhD, Senior Registrar.
J. K. Kristensen, MD, PhD, Consultant.

Requests for reprints to: A. Bødker, Nyelandsvej 88, DK-2000 Copenhagen F, Denmark.

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Varicocele and Puberty—the Critical Factor?

G. G. WYLLIE

Department of Surgery, Adelaide Children's Hospital, North Adelaide, Australia

> "*The cause-and-effect relationship between varicocele and male infertility is uncertain*". (Turner, 1983)

Summary—In some boys variococele develops before puberty, when the testis is immature and vulnerable. Based on testicular size, evidence suggests that the time of development of a varicocele in relation to puberty may be the critical factor in the subsequent development of infertility. The recognition and treatment of an early-developing varicocele may help to reduce the infertility associated with this condition.

The purpose of this report is to draw attention to the effect on the development of the testis in a boy whose varicocele develops before puberty, and to suggest that he may become the man who will present with infertility.

Patients and Methods

In the Adelaide Children's Hospital 10 boys with varicocele were treated between January 1981 and June 1983. All had left-sided varicocele. In each boy the operation performed was ligation of the branches of the spermatic vein above the internal inguinal ring.

It was soon recognised that these boys had a difference in the size of their testes. In 9 boys the left testis was smaller than the right, as measured by an orchiometer. Measurements were made by measuring the size of each testis separately, and then by holding the testes together in the centre of the scrotum so that the sizes could be compared. Also, in those 9 boys the left testis was softer than normal.

In 4 of the boys the testes were of pre-adolescent size—3 or 4 ml. In 6 boys the testes were 6 to 12 ml in volume, but none had pubic hair. Figure 1 is a typical example. Thus the stage of development of sex characteristics in all boys was Stage 1 or early Stage 2 (Tanner, 1978).

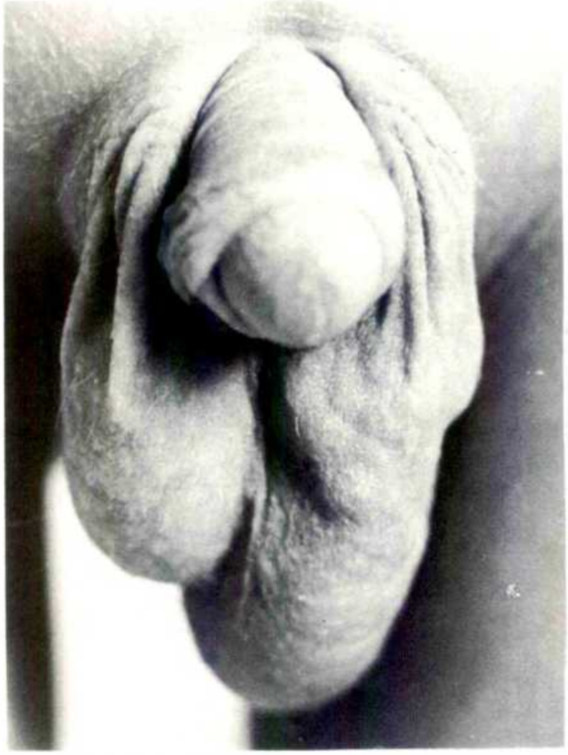

Fig. Varicocele in a pre-pubertal boy.

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The Table shows the testicular sizes of the 10 boys at initial consultation. Thus in several boys there were large differences in the size of the testes and it seemed reasonable to associate those differences with the presence of a varicocele, as there was no other explanation. The author has seen a number of boys with a capillary haemangioma on one side of the scrotum, and in them the testis on the side of the angioma has been smaller and softer than the opposite testis. This suggests that the development of an immature testis may be affected adversely when there is increased blood flow in the vicinity.

Table Testicular Sizes at Presentation

Patients	*Age*	*R. testis (size in ml)*	*L. testis (size in ml)*
1. S. R.	11	3	2.5
2. A.F.	10	3.5	2.5
3. B.L.	10	3	3
4. G.H.	13	8	4
5. F.P.	12	8	4
6. B.H.	12	8	6
7. A.M.R.	11	12	8
8. A.K.	12	8	6
9. B.T.	11	3	2.5
10. N.B.	13	12	10

Because it is known that testicular sizes may differ slightly during adolescence (Daniel *et al.*, 1982), 50 healthy boys were examined at two Adelaide schools. They were aged between 10 and 13 years and the measurements were made as described. The size of their testes varied between 2 and 12 ml, but in none was any difference found in the size of the two testes.

Results

In only three boys has the interval since operation allowed for significant testicular development. In Case 1 each testis was 10 ml in volume 2 years after operation. In Case 7 the right testis was 20 ml and the left 18 ml in size after 1½ years, while in Case 9 each testis was 8 ml in volume after 15 months.

Discussion

Most of the investigations of infertile men with varicocele have concentrated on histological, radiological and biochemical assessments. Very few authors have mentioned the size of the testes in these men. However, Lipshultz and Corriere (1977) found that the testes in a group of infertile men with varicocele were smaller than in a comparable infertile group without varicocele. Tulloch (1962) reported that the testis on the side of a varicocele was smaller and softer than normal, whereas the opposite testis was normal in size but softer than usual.

The incidence of early-developing varicoceles is probably about 15% of all youths who develop varicocele. An investigation of Danish schoolboys by Øster (1971) showed that about 15% of those who developed a varicocele were pre-pubertal at the time. A similar study of schoolboys in Leicester by Horner (1960) suggested a comparable incidence of 17%. However, Horner included in his group "Puberty not Established" some boys who had pubic hair and thus might have had well developed testes. The incidence of early-developing varicoceles may have been less than 17% in this group of English schoolboys. However, in the majority of each group a varicocele developed after puberty.

Thus in the majority of youths with varicocele the testis would have grown to adult size (20-25 ml) before a varicocele developed, whereas there is evidence that a varicocele which develops when the testis is immature adversely affects its growth as measured by testicular size. Experience with cryptorchidism is that a small, soft testis does not develop to normal adult size (Wyllie, 1984). Indeed, mean testicular volume is a good index of reproductive function as it can be strongly correlated with sperm counts (Werder *et al.*, 1976).

Had these boys not been treated it could be expected that they would reach adult life with the left testis smaller and softer than normal, which is similar to the findings in infertility clinics of Lipshultz and Corriere (1977) and of Tulloch (1962).

Ibrahim *et al.* (1977) have shown that in adult patients with varicocele presenting because of infertility, the pathological changes are bilateral, though more advanced on the varicocele side. That evidence supports the observation which Tulloch (1962) reported.

Heinz *et al.* (1980) performed testicular biopsies when treating youths with varicocele who were aged 12 to 16 years. They found morphological changes similar to those described in adult patients with varicocele who presented to infertility clinics (McFadden and Mehan, 1978). These changes included quantitative and qualitative deviations of spermatogenesis from normal, an increased tendency of germinal epithelium to desquamate, frequent signs of degenerative changes of the walls of individual tubules, interstitial oedema, and focal interstitial fibrosis. Moreover, these changes were similar, though less marked, in the opposite testis.

Thus, based on the measurement of testicular size it seems reasonable to assume that it is a varicocele which develops before puberty which may lead to subsequent infertility. The prevention of infertility associated with this lesion could depend on the recognition of a varicocele which develops in a boy before puberty, and the early surgical correction of that varicocele.

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The Author

G. G. Wyllie, FRCS, FRACS, Surgeon, Department of Surgery, The Adelaide Children's Hospital Inc., North Adelaide, South Australia 5006.

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Abdominal Pain as a Presenting Symptom of Male Germ Cell Tumour

PATRICIA HOGAN, H. SMEDLEY and K. SIKORA

Department of Radiotherapy and Ludwig Institute for Cancer Research, Addenbrooke's Hospital, Cambridge

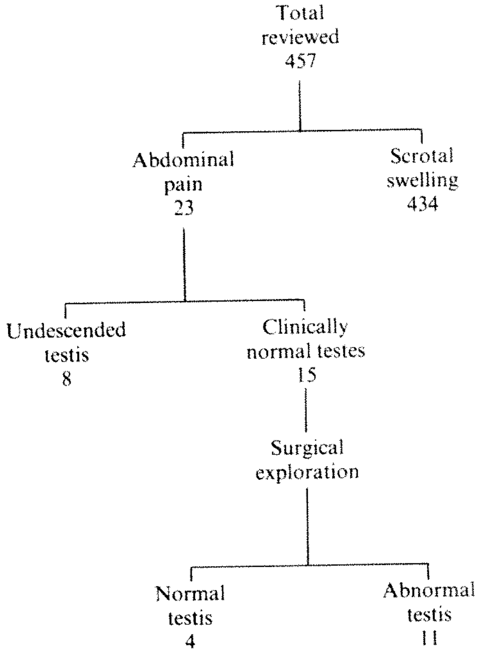
Summary—Twenty-three patients who presented with abdominal pain and were found to have germ cell tumours have been reviewed. The overall survival of these patients was no different from the survival of those presenting with testicular swellings. Intra-abdominal germ cell tumour remains an important differential diagnosis of abdominal pain in men.

Most patients with testicular cancer present with swelling in the scrotum. However, a significant minority present with abdominal pain caused by an intra-abdominal primary tumour. These patients are usually referred to general surgeons, often in an emergency, and may have extensive intra-abdominal disease. The advent of precise staging procedures, megavoltage radiotherapy and effective chemotherapy has resulted in a dramatic improvement in the survival of patients with testicular cancer in general (Einhorn and Donohue, 1977; Peckham *et al.*, 1979). We have reviewed the outcome of 23 patients presenting to a single centre with abdominal pain and compared it with those presenting with testicular swelling.

Patients, Methods and Results

Four hundred and fifty-seven patients presented to this department with testicular cancer between 1960 and 1983. The patients were identified by using the East Anglia Cancer Registration Bureau. Their records were reviewed and 23 (5%) were found to have presented with abdominal pain. In most cases the pain was poorly localised and had been present for an average of 6 months (range 1 day-1 year). None of these patients had testicular symptoms.

Table Analysis of Patients



Two groups of patients were recognised. Those in the first group were known to have uncorrected maldescent of one testis. Those in the second group gave no history of testicular abnormality. The eight patients in the first group were investigated preoperatively by either abdominal ultrasound or intravenous urography. Intra-abdominal masses were defined in all cases. Fifteen patients had no history of maldescent and provisional diagnoses included acute appendicitis (5), peptic ulceration (3)

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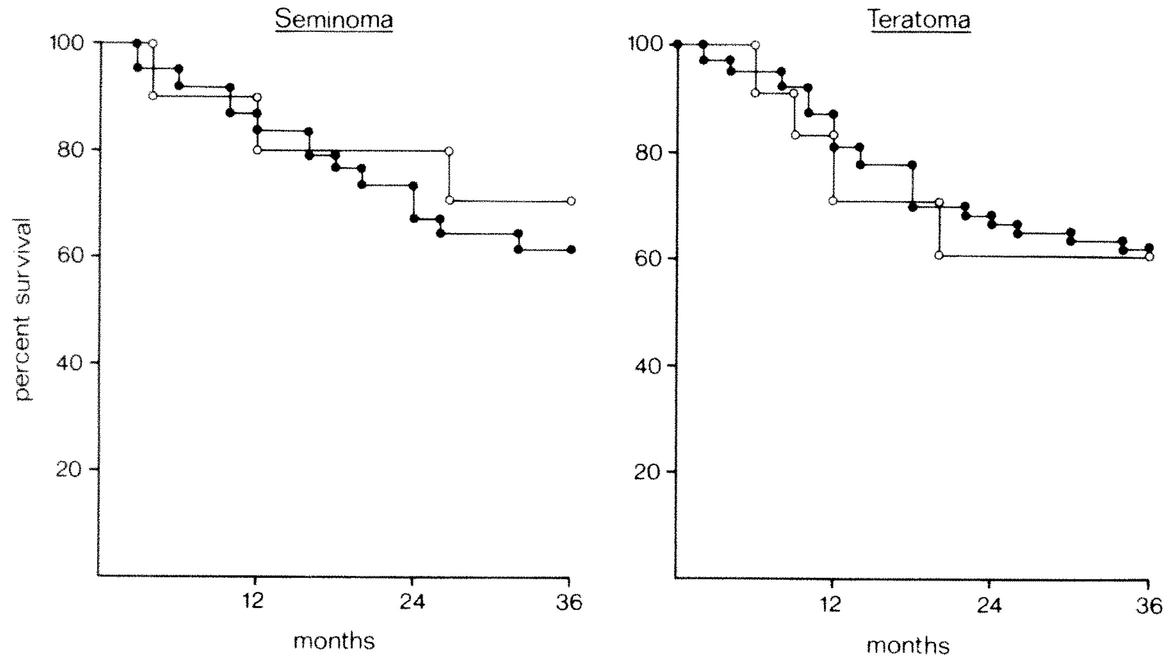

Fig. Age-corrected survival curves of patients with scrotal (●) and intra-abdominal (○) presentation of testicular cancer.

and lymphoma (3). All 23 patients underwent laparotomy to establish the cause of their pain. Intra-abdominal masses were found and biopsied. Subsequent histological examination revealed seminoma in 11 patients and teratoma in 12. In all eight of the patients with uncorrected maldescent the abdominal testis was thought to be the source of the primary. In 11 of the 15 patients with apparently normal testes the testis on the involved side was explored via the inguinal route at the time of laparotomy and found to be macroscopically abnormal. Biopsy of the abnormal areas revealed a neoplasm of the same histological type as the intra-abdominal disease (Table). Staging investigations were performed on all patients and resulted in downstaging from stage I to III in three patients and from II to IV in two.

Treatment protocols for testicular tumours have changed over the years and our patients were treated according to the protocol used by the department at the time. Although radiotherapy remains a vital part of treatment, the increasing use of chemotherapy, in particular cisplatin, has altered the prognosis dramatically, especially for patients with advanced disease (Newlands *et al.*, 1983). For this reason we have compared results obtained in patients presenting with abdominal pain with those with scrotal presentation over the same period of time (Fig). Survival curves were constructed using the standard actuarial method (life table analysis). No difference in overall outcome was observed.

Discussion

The outlook for testicular cancer has improved considerably. There now appears to be a similar chance of survival in patients presenting with abdominal pain and those with a classical presentation. All abdominal masses represented either local spread from malignant maldescended testes or metastatic spread from microscopic areas of malignancy in apparently normal testes. Little information is available on the prognosis of patients with undescended testes that have undergone malignant change. Although the numbers are small, our series shows that malignancy arising primarily in the abdomen or within the undescended testis appears to carry no worse a prognosis than malignancy arising in a scrotal testis.

Patients may present with a long history of abdominal symptoms (Munro *et al.*, 1983). Clearly normal testes do not exclude intra-abdominal testicular malignancy, which should be included in the differential diagnosis of any male patient presenting with a history of unexplained abdominal pain.

Acknowledgements

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The Authors

Patricia Hogan, MA, MB, BChir, Senior House Officer, Department of Radiotherapy.

H. Smedley, FRCR, Senior Registrar, Department of Radiotherapy.

K. Sikora, MRCP, FRCR, Director, Ludwig Institute for Cancer Research.

Requests for reprints to: K. Sikora, Ludwig Institute for Cancer Research, MRC Centre, The Medical School, Hills Road, Cambridge CB2 2QH.

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The Value of Fine Needle Aspiration Cytology in the Management of Metastatic Germ Cell Tumours

R. T. D. OLIVER, W. J. HIGHMAN, M. J. KELLETT, O. M. CURLING and J. E. DACIE

Medical Oncology Unit, Institute of Urology, the London and St Bartholomew's Hospital Medical Colleges; Departments of Cytology and Radiology, Institute of Urology, St Peter's Hospitals and St Bartholomew's Hospital, London

Summary—Review of 19 patients with advanced metastatic malignant teratomas has revealed five serious complications possibly related to the surgical biopsy procedure, three of which led to the patient's death.

Preliminary results from a small series of patients diagnosed by fine needle aspiration (FNA) cytology suggest that this procedure is a reliable alternative method for diagnosing these patients. In addition, when used after chemotherapy this procedure may save patients with residual malignancy from having to undergo post-treatment surgical staging. However, the absence of malignant cells in the aspirate cannot exclude malignancy because of the focal distribution of residual tumour in these masses.

The last decade has witnessed a dramatic improvement in the survival of patients with metastatic germ cell tumours of the testis (Einhorn and Donohue, 1977; Newlands *et al.*, 1983; Peckham *et al.*, 1983). Today most of the deaths are in patients who present with advanced disease as measured by tumour volume or tumour marker (AFP and beta-HCG) level (Germa-Lluch *et al.*, 1980; Peckham *et al.*, 1981), all of which are associated with delay from first symptom (Oliver and Evans, in preparation).

Germ cell tumours vary markedly in their growth rate. At one extreme, patients with metastatic trophoblastic tumours may be dead, if left untreated, in less than 6 weeks with tumour volumes doubling every 5 to 6 days (Garreta *et al.*, 1970). At the other extreme, occasional patients with seminoma may delay for up to 5 years without developing metastases. Despite this extreme variability, delay in diagnosis is an adverse prognostic factor in terms of both the risk of developing metastases and in the chance of cure by cytotoxic drugs once metastases have developed. Although the 7 to 10 days' delay in treatment necessary for uncomplicated healing of an inguinal wound are unlikely to make a major difference to survival chances, a surgical complication developing after a difficult laparatomy or thoracotomy undertaken to diagnose a primary tumour may cause considerable delay. It was following a death from such a complication associated with the effects of chemotherapy that the following investigation of the role of fine needle aspiration cytology was initiated.

Patients and Methods

Treatment schedules and survival analyses on these patients have been published in detail elsewhere (Oliver *et al.*, 1983).

Any patient who presented with metastatic disease, whether or not there was an obvious tumour in the testicle, had fine needle aspiration of the mass and serum levels of AFP and HCG estimated as an emergency. FNA cytology was also carried out in any patient who had a residual mass at the site of previous disease after completion of

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

chemotherapy in whom post-treatment surgical staging was indicated.

Fine needle aspiration was performed using a sharp 23 gauge needle. Negative pressure was maintained while the needle was moved back and forth in the mass and released before the needle was withdrawn. Aspirations were made from several sites in large masses in an attempt to ensure adequate sampling.

Palpable masses were aspirated by direct puncture. Three principal techniques were used for intra-thoracic or intra-abdominal masses (Table 1).

Table 1 Techniques for fine needle aspiration biopsy

1. Palpable mass—direct puncture
2. Nodes opacified by lymphography—fluoroscopic guided biopsy
3. CT demonstration of lymphadenopathy
   (a) direct CT controlled FNA
   (b) CT scan used as a "map" for FNA under fluoroscopic control

Results

The results and complications of investigations and treatment in the series of teratoma patients are summarised in Table 2. The early deaths on chemotherapy, possibly attributable to the surgical biopsy, occurred firstly in a patient with ascending thrombosis from an abscess that developed on treatment in an inguinal wound which had been healed at the time treatment was commenced. This led to the patient's death from renal vein thrombosis. Two further patients requiring laparotomy for diagnosis of a palpable abdominal mass died from leucopenic sepsis arising from unsuspected intra-abdominal infection which only became manifest after treatment was started.

Table 2 Impact of Diagnostic Procedure on Results of Treatment of Patients with Large Volume Malignant Teratoma Metastases

	No.	*Alive NED*	*Early treatment-related death*	*Serious complications related to biopsy*
Surgical excision biopsy	19	6	3	2
Positive fine needle biopsy or positive tumour marker	5	4	—	—

NED = No evidence of disease.

The first serious complication related to the surgical procedure was complete duodenal obstruction necessitating intravenous feeding for 6 weeks. This was due to tumour invasion following accidental perforation of the duodenum during biopsy at laparotomy for an abdominal mass in a patient with a regressed primary tumour. The second complication was large bowel obstruction from adhesions following diagnosis after a laparotomy.

The FNA aspiration biopsy findings are shown in Table 3. In 7 of 10 patients undergoing aspiration biopsy at the time of presentation, viable malignancy compatible with germ cell tumour was demonstrated. Only one of nine patients undergoing FNA biopsy at the completion of treatment had evidence of viable malignancy. This was confirmed by subsequent follow-up or surgical excision biopsy, with the exception of one patient in whom an area of mature teratoma was demonstrated after surgical excision of the mass.

Table 3 Summary of Findings on Fine Needle Aspiration Biopsy in Patients with Germ Cell Tumours

	Positive	*No evidence of malignancy*
FNA biopsy before chemotherapy	7	3
FNA biopsy assessment after chemotherapy	1	8

Cytological Features

These are shown in Figures 1 to 5. Aspirates were taken from testicular tumours in the fresh surgical specimens to provide a guide for comparison with aspirates from the metastases. There was close morphological similarity between aspirates from the primary and metastatic tumours. There were also clear-cut morphological differences between different types of tumour which enabled a diagnosis of tumour type to be made. An interesting finding was nuclear bloating and degeneration demonstrated in the aspirate from a seminoma deposit in the lung following a course of cisplatin (Fig. 5).

Discussion

Because of the operative complications of the

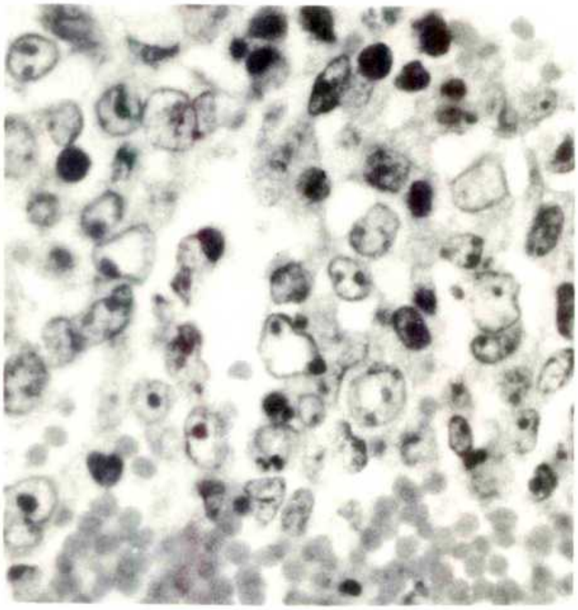

Fig. 1 Aspirate from para-aortic lymph node of patient with malignant teratoma undifferentiated.

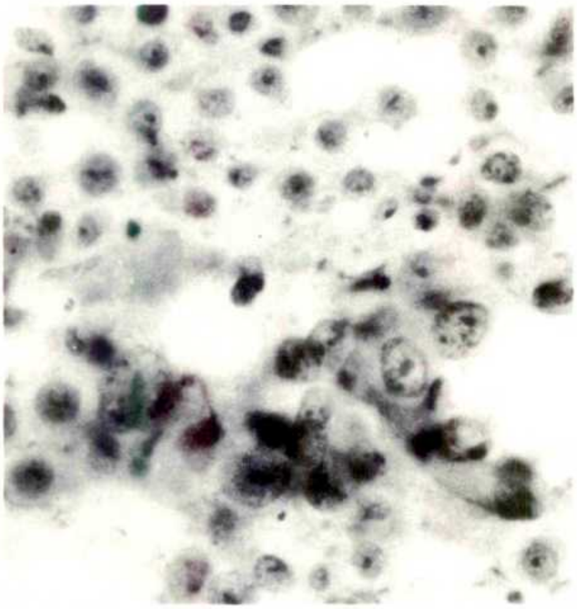

Fig. 2 Aspirate from supraclavicular lymph node of patient with seminoma.

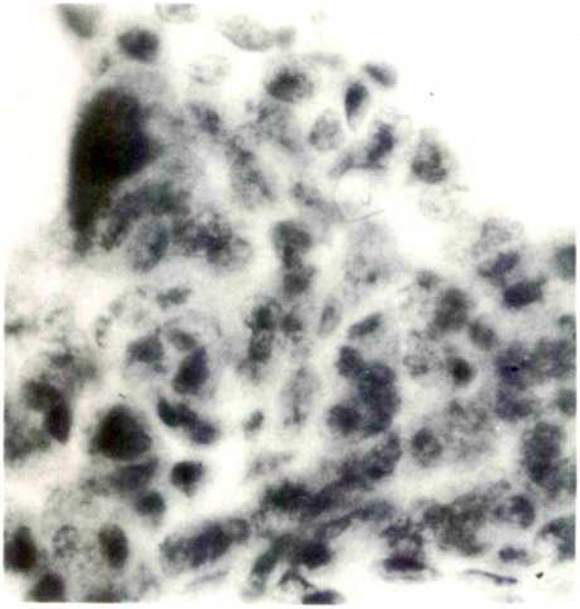

Fig. 3 Aspirate of lung metastasis of patient with malignant teratoma trophoblastic.

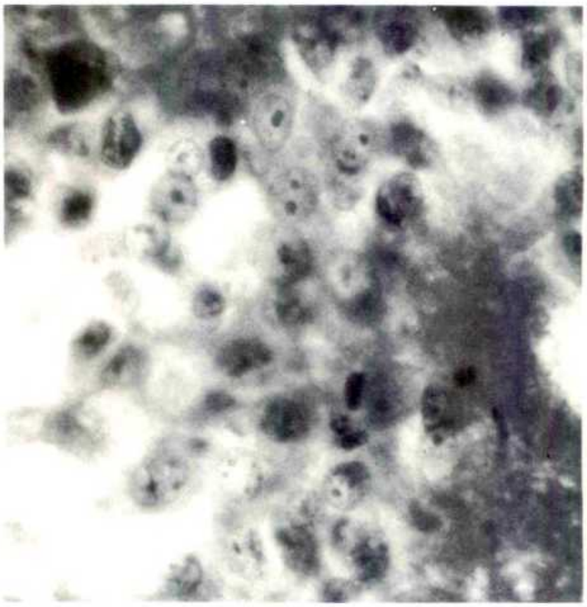

Fig. 4 Aspirate of lung metastasis of patient with seminoma before chemotherapy.

surgical procedures needed to obtain histological material for diagnosis of patients with germ cell tumours. FNA biopsy was introduced in conjunction with emergency estimation of tumour markers AFP and HCG (and more recently placental alkaline phosphatase, a marker of seminoma (Tucker *et al.*, in preparation)) for all patients who presented with obvious metastases. Though it is not possible to obtain enough material to establish all of the features discernible in sections examined by light

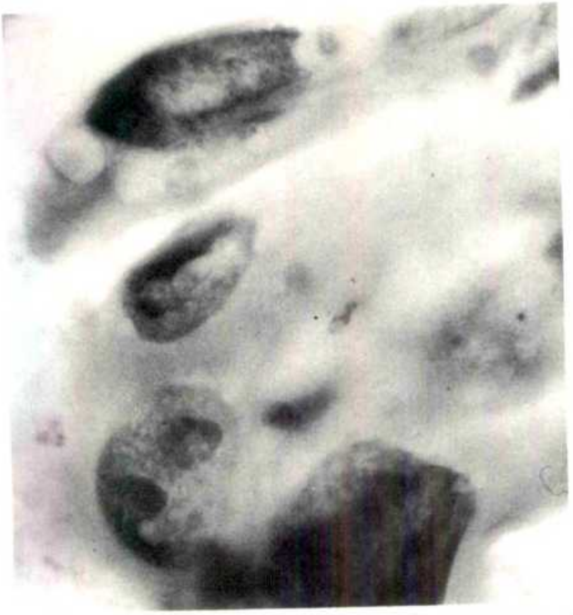

Fig. 5 Aspirate of same metastasis following failure of chemotherapy.

microscopy, this limited experience does suggest that the findings of FNA biopsy are sufficiently reliable to save the patient from a major surgical procedure prior to starting chemotherapy. This is important as most of these patients will ultimately need surgery after treatment to remove residual masses. For the future, added confidence will come with the availability of immunocytochemical staining techniques to demonstrate tumour marker synthesis in the aspirated cells.

The value of aspiration biopsy after treatment is still limited but it has enabled one patient to avoid an unnecessary thoracotomy to prove that he had drug resistant tumour in the face of negative tumour markers in the blood. Of possibly equal importance in the patients who ultimately were found to have no evidence of malignancy on follow-up has been the confidence that as there was no gross tumour present it was safe to postpone surgery for 4 to 6 weeks, to enable the patient to recover from the effects of chemotherapy. Radiology could be repeated to establish that the mass was not shrinking rapidly. However, review of the masses excised in our previously reported series of patients undergoing post-treatment surgical staging has demonstrated that the residual malignancy never constituted 100% of the mass and often made up less than 10%. This accounts for the problem of tumour sampling during FNA aspiration, where a tumour constitutes only a fraction of the whole specimen. A negative report does therefore not exclude tumour.

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The Authors

R. T. D. Oliver, MD, FRCP, Reader in Oncology, Institute of Urology, the London and St Bartholomew's Hospital Medical Colleges.

W. J. Highman, FRCPath, Consultant Cytologist, Institute of Urology and St Peter's Hospitals.

M. J. Kellett, DMRD, Consultant Radiologist and Director, Diagnostic X-ray Department, Institute of Urology and St Peter's Hospitals.

O. M. Curling, MRCS, LRCP, Consultant Cytologist, St Bartholomew's Hospital.

J. E. Dacie, MRCP, MRCS, Consultant Radiologist, St Bartholomew's Hospital.

Requests for reprints to: R. T. D. Oliver, Department of Urology, The London Hospital Medical College, Whitechapel, London E1 1BB.

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Post-treatment Fertility in Patients with Testicular Cancer

I. Influence of Retroperitoneal Lymph Node Dissection on Ejaculatory Potency

SOPHIE D. FOSSÅ, S. OUS, T. ÅBYHOLM and M. LOEB

General and Surgical Departments, Norwegian Radium Hospital; Gynaecological Department, Rikshospitalet, Oslo, Norway

Summary—"Dry ejaculation" occurred in none of 15 patients with testicular cancer treated by right-sided retroperitoneal lymph node dissection (RLND). After left-sided and bilateral RLND, "dry ejaculation" was observed in 7/21 and 51/61 men respectively. Twelve of 21 patients with "dry ejaculation" or small volumes of seminal fluid had true retrograde ejaculation. In 7 of 10 men the ejaculatory volume increased significantly after treatment with imipramine chloride. Four men impregnated their wives during treatment with the drug.

Without impairing the results of therapy it is possible to spare fibres from the sympathetic chains and pre-sacral plexus during RLND due to testicular cancer, thus preserving fertility in at least 40% of patients.

Testicular cancer occurs most frequently in the third to fifth decade. About 80 to 90% of all patients with this disease can now be cured. The question of treatment-induced infertility therefore becomes important for most of these patients.

Modern therapy for testicular cancer may be followed by disturbances of ejaculatory potency, of hormone production and spermatogenesis. This study investigated the treatment-related disturbances of ejaculation and the possibility of reducing the fertility problems resulting from "dry ejaculation".

Patients and Methods

Principles of treatment

At the Norwegian Radium Hospital cis-platin was introduced in 1978 into the primary treatment of metastatic testicular cancer, clinical stage IIB or more (Peckham *et al.*, 1981). In the period 1978 to 1980 all patients received induction treatment with four cycles of CVB (cis-platin 20 mg/m^2 days 1-5, vinblastine 0.12-0.15 mg/kg days 1 and 2, bleomycin 30 mg days 2, 5 and 15, every third week) followed by four cycles of consolidation treatment (CVB + doxorubinic hydrochloride + cyclophosphamide + vincristine) and maintenance therapy (1 year) (CCNU and vinblastine). Patients who responded to treatment received post-chemotherapy irradiation to the initial tumour-bearing regions (Klepp *et al.*, 1984). After 1980 the consolidation and maintenance chemotherapy and the irradiation were replaced by bilateral retroperitoneal lymph node dissection (Fosså *et al.*, 1984b) (Fig. 1). If no metastatic growth was found in the contralateral iliac region, the lymph nodes below the iliac bifurcation were not resected. Lymph nodes above the renal vessels were removed only if evidence of metastases was demonstrated in this region during the operation. If possible, fibres from the contralateral sympathetic chain were preserved during the operation. If residual malignant tumour tissue was found in the operation specimen, second-line treatment comprised combination chemotherapy with doxorubicin hydrochloride, VP16, ifosfamide and, in selected cases, radiotherapy.

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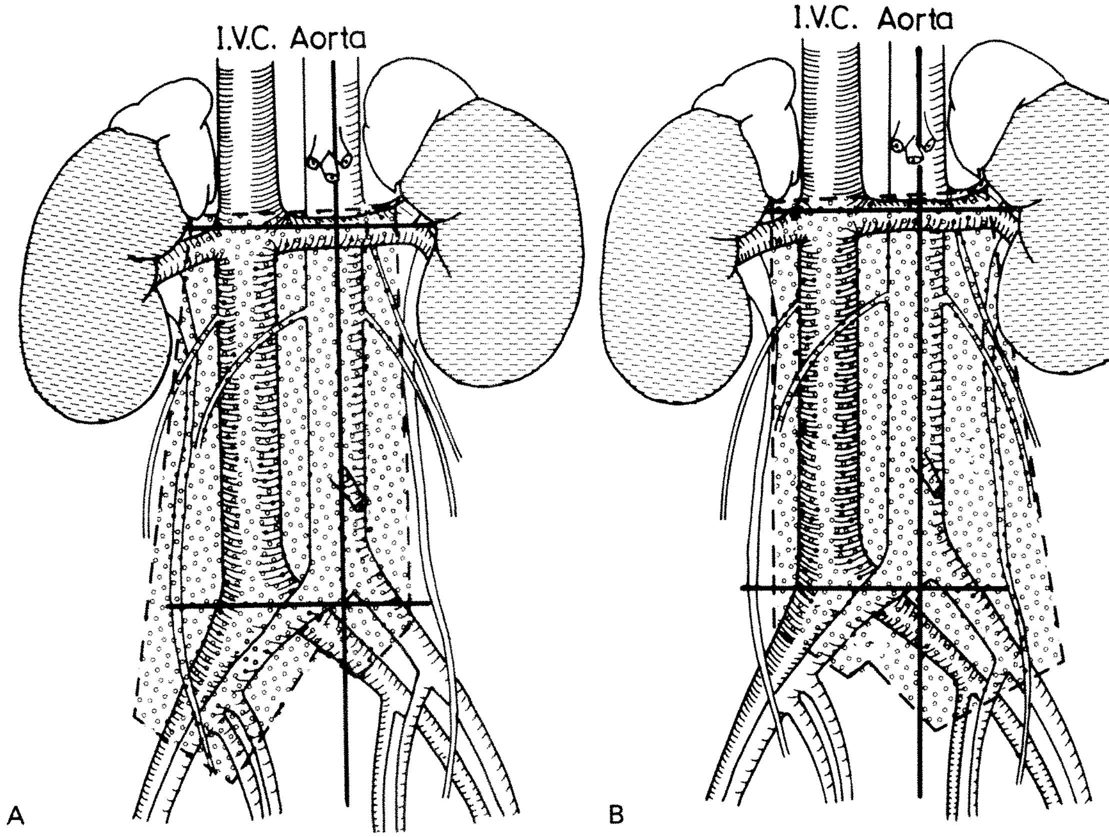

Fig. 1 Extent of *bilateral* retroperitoneal lymph node dissection in patients with (A) right-sided and (B) left-sided non-seminomatous testicular cancer (IVC: inferior vena cava).

From 1979 onwards, patients with non-seminomatous testicular cancer clinical stage I and IIA had a primary retroperitoneal lymph node dissection (Fosså *et al.*, 1984c). A unilateral dissection was done if no metastases were found per-operatively (pathological stage (PS, I) (Fig. 2). Bilateral RLND (Fig. 1) was performed if retroperitoneal lymph node metastases were found during the operation (PS II), followed by three cycles of CVB.

The present study was carried out on 97 patients (mean age 30 years, range 15.2-59.5) who underwent retroperitoneal surgery according to the above principles and who were without recurrence at the time of fertility evaluation (median observation time 22.3 months) (Table 1). In six patients with clinical stage I disease the metastases were not detected per-operatively but by the final histological examination of the operation specimen. These

Table 1 Details of Treatment

		Number of patients
RLND* only		31
Right-sided	14	
Left-sided	16	
Bilateral (left)**	1	
RLND + CVB° + other cytotoxic treatment +		66
Right-sided	1	
Left-sided	5	
Bilateral (right)**	23	
Bilateral (left)**	37	
Total		97

* Retroperitoneal lymph node dissection.
** ( ) : Side of the primary tumour.
° : Cis-platinum, vinblastine, bleomycin.
+ : Other cytostatics and/or radiotherapy.

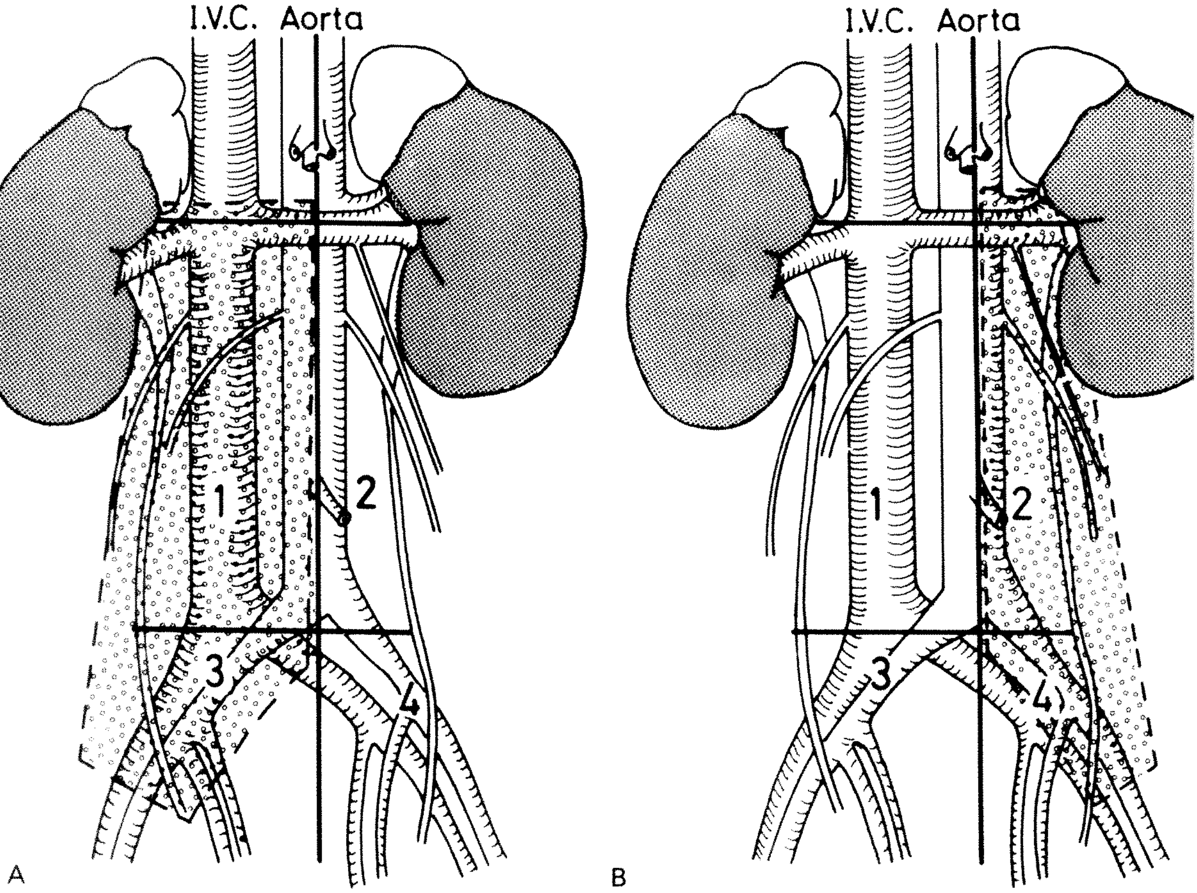

Fig. 2 Extent of (A) right-sided and (B) left-sided *unilateral* retroperitoneal lymph node dissection in patients with non-seminomatous testicular cancer (IVC: inferior vena cava).
1: Cavo/inter-cavo-aortic region.
2: Pre/para-aortic region.
3: Right iliac region.
4: Left iliac region.

unilaterally-treated patients received three cycles of CVB post-operatively. One patient with clinical stage I disease, in whom two totally necrotic lymph node metastases were removed by primary bilateral RLND, did not receive adjuvant CVB treatment.

From 1 to 3 years after the operation, the patients were asked about their post-operative ejaculatory potency. Their answers were recorded as presence or absence of "dry ejaculation".

Thirty-eight patients had sperm analysis after orchiectomy before further treatment. Twenty-six patients without "dry ejaculation" agreed to have at least one post-treatment sperm analysis performed 1 to 3 years after discontinuation of all treatment.

The sperm analysis comprised evaluation of the volume of the ejaculate (obtained by masturbation after at least 3 days' sexual abstinence), the number of sperm cells per ml, the motility index (Fosså *et al.*, 1984a) and the percentage of morphologically abnormal cells. The main parameter for the present study was the volume of the ejaculate. Together with a sperm analysis a blood sample from the peripheral arm vein was analysed for serum LH, FSH and testosterone by previously reported methods (Fosså *et al.*, 1980).

Finally, 10 patients with "dry ejaculation" or very small volumes of ejaculate (< 1 ml) were treated with imipramine chloride 25 mg × 3 daily orally for 2 weeks. All patients were interviewed about the effect of this preparation. If possible a sperm analysis was performed before (in the post-masturbation urine) and after treatment with imipramine.

Results

After right-sided RLND none of the 15 patients complained of "dry ejaculation" (Table 2). One-third of those who were treated by left-sided RLND had "dry ejaculation". Ten of the 61 patients subjected to bilateral RLND had normal or nearly normal ejaculation.

Five of 26 patients who claimed to have normal or nearly normal ejaculation had an ejaculatory volume less than 1 ml. Three of these had sperm cells in the post-masturbation urine (Table 3). In addition, sperm cells were found in the urine of 9 of 16 patients with complete "dry ejaculation".

The mean ejaculatory volume remained unchanged after right-sided unilateral RLND compared with the pre-treatment situation (Table 4). On the other hand, the mean volume of the ejaculate tended to decrease in patients who had undergone left-sided or bilateral RLND. (Patients with "dry ejaculate" are excluded from Table 4). The frequency of fatherhood (without sympathico-mimetic treatment, see below) was: after right-sided RLND: 4 patients; after left-sided RLND: 6 patients; after bilateral RLND: 0 patients.

After treatment with imipramine the ejaculatory volume increased in 7 of 10 patients (Table 5). Five patients agreed to undergo sperm analysis during treatment (nos 3, 4, 6, 7, 9). Normospermia (>10 million sperm cells/ml) was demonstrated in four patients, whereas the fifth (no. 3) was azoospermic. This patient had a highly increased serum FSH. In patient no. 7 the first trial with imipramine failed to reverse his "dry ejaculation". At that time the post-masturbation urine contained no sperm cells. A second trial was undertaken after 6 months: normal ejaculation and normospermia were noted.

Four patients (nos. 4, 5, 6 and 9) became fathers during treatment with imipramine. Patient no. 4 had a post-chemotherapy bilateral RLND. Patient no. 5 was treated by a left-sided RLND for PS I. Before the imipramine trial this latter patient had, without success, tried to father a child by artificial insemination using his deep-frozen pre-treatment seminal fluid. Patients nos 6 and 9 had undergone primary bilateral RLND for PS II followed by three CVB cycles.

Table 2 RLND and "Dry Ejaculation"

RLND	*"Dry ejaculation" Number of patients*		
	Yes	*No*	*Total*
Unilateral:			
Right-sided	0	15	15
Left-sided	7	14	21
Bilateral:			
(Right)*	17	6	23
(Left)*	34	4	38
Total	58	39	97

* ( ): Side of the primary tumour.

Table 3 Sperm Cells in the Post-masturbation Urine (True Retrograde Ejaculation)

Dry ejaculation	*No. of patients*		
		Sperm cells	
	Total	*Present*	*Absent*
No, but volume < 1 ml	5*	3	2
Yes	16	9	7
Total	21	12	9

* 1 after right-sided
1 after left-sided } RLND
3 after bilateral

Discussion

"Dry ejaculation" results either from lack of seminal emission (seminal transport into the posterior urethra) or from true retrograde ejaculation

Table 4 Ejaculatory Volumes (Mean) Before and After RLND

RLND	*Volume (ml) (Number of patients)*	
	Before RLND	*After RLND*
Unilateral:		
Right-sided	4.1 (6)	3.9 (10)
Left-sided	3.8 (4)	2.8 (9)
Bilateral:		
(Right)*	4.5 (6)	1.5 (4)
(Left)*	3.8 (21)	2.9 (3)

* ( ): Side of the primary tumour.

Table 5 Ejaculatory Potency Before and After Imipramine

Patient No.	*RLND*	*Serum FSH (iu/l)*	*Ejaculation volume*		*Number of sperm cells mill/ml*	*Sperm cells in the urine*
			Before Imipramine	*After Imipramine*		
1	Bilateral	27.8	0	0	Not evaluated	no
2	Unilateral (right)	16.8	0.5	(+)	Not evaluated	yes
3	Bilateral	50.1	0.5	4.3	0	no
4[+]	Bilateral	22.6	0	2.5	38	yes
5[+]	Unilateral (left)	6.7	0	(+)	Not evaluated	yes
6[+]	Bilateral	13.8	0.5	3.0	42	yes
7	Bilateral	7.8	0	2.0	53	no
8	Bilateral	14.9	0	0	Not evaluated	yes
9[+]	Bilateral	10.7	0.5	4.0	65	yes
10	Bilateral	4.7	0	0	Not evaluated	yes

(+)* : Not evaluated by sperm analysis, subjectively improved.

[+] : Fatherhood during imipramine treatment.

(ejaculation = seminal expulsion from the urethral meatus) (Benson *et al.*, 1981). This condition is seen in 80 to 100% of patients undergoing RLND (Kom *et al.*, 1971; Kedia *et al.*, 1977). During bilateral RLND the fibres from the sympathetic chains and from the pre-sacral plexus are usually permanently interrupted. These fibres regulate emission and true ejaculation. However, there is considerable individual variation in the innervation of ejaculation. As the RLND becomes more radical, the frequency of "dry ejaculation" increases. Infertility due to "dry ejaculation" may be avoided by preservation of one side's sympathetic chain and/or a considerable amount of the pre-sacral fibres (Narayan *et al.*, 1982).

Is it justifiable to preserve some of the sympathetic fibres during RLND in patients with testicular cancer, thus preserving normal ejaculation and fertility? This should be balanced against an optimal therapeutic result as the primary goal of treatment.

About 70 to 90% of the primarily operated patients with non-seminomatous testicular cancer clinical stage I are tumour-free. In addition, 30 to 40% of the patients with advanced disease are rendered tumour-free by modern cis-platin-based chemotherapy. In these patients RLND is primarily a diagnostic procedure. It seems therefore justified to use a more limited operative approach which preserves, at least partially, fibres from the contralateral sympathetic chain and/or the pre-sacral plexus.

Following this treatment policy, 39 of our 97 patients have reported normal ejaculation after RLND, confirming the promising results of Narayan *et al.* (1982), who also tried to spare the pre-sacral plexus during RLND. Twenty-five of their 55 patients had normal ejaculation after RLND. Admittedly, some of the patients with "normal" ejaculation objectively had a very small volume of seminal fluid. We have no definite explanation for the significant differences in frequency of "dry ejaculation" in patients after right-sided compared with left-sided RLND. However, one reason may be that more fibres of the pre-sacral plexus are spared during right-sided RLND than during the left-sided operation.

So far, we have treated 64 patients with PS I by unilateral RLND and 38 patients with PS II by bilateral RLND. In addition, eight patients with PS II were operated upon unilaterally before receiving adjuvant CVB. After a median observation time of 22 months, only two patients with PS I have relapsed, none of them in the retroperitoneal space. Our therapeutic results using more limited secondary RLND after cis-platin-based induction chemotherapy are comparable with those reported by other authors who performed more extensive secondary bilateral RLND (Fosså *et al.*, 1984b; Klepp *et al.*, 1984).

From this study it cannot be determined to what extent the lack of "dry ejaculation" 1 year or more after RLND is due to primarily preserved ejaculation or due to regeneration of sympathetic fibres during the follow-up period. It is, however, our impression that regeneration of sympathetic nerves occurs only rarely. Only exceptionally was ejaculatory potency regained in patients who 3 months after RLND had "dry ejaculation".

In the individual patient with "dry ejaculation" after RLND it is always questionable to what extent the disturbance is due to lack of emission or to true retrograde ejaculation or both. Kedia *et al.* (1977) think that emission disturbances are the more important factor in "dry ejaculation". Our observations do not confirm this view. True retrograde ejaculation occurs frequently in patients with "dry ejaculation" after RLND. Our results also support the observations of Narayan *et al.* (1982), who reported a positive effect of sympathico-mimetic drugs in 5 of 10 patients with "dry ejaculation".

Our figures probably reflect a minimum frequency of retrograde ejaculation. The presence of sperm cells in the urine, in the present study the only indicator for retrograde ejaculation, is influenced not only by disorders of seminal transport but also by cytotoxic treatment given to the individual patient. In some of our patients the lack of sperm cells in the urine may be due to lack of spermatogenesis, even if the patient had true retrograde ejaculation. Perhaps the number of patients with true retrograde ejaculation would have been larger if the post-masturbation urine had been analysed for the presence of fructose (Kedia *et al.*, 1977).

At least one trial with sympathico-mimetic drugs should be performed in patients with "dry ejaculation" who wish to become fathers and who have a normal serum FSH, indicating normal spermatogenesis. Our results thus confirm previous reports on patients with testicular cancer who achieved fatherhood after RLND by using sympathico-mimetic drugs (Kelly and Needle, 1979; Nijman *et al.*, 1982).

In patients with testicular cancer RLND should not be unnecessarily extensive. Without adversely affecting the results of therapy it is possible to spare the contralateral sympathetic chain and/or the sympathetic fibres of the pre-sacral plexus in a considerable number of patients, thus preserving ejaculatory potency in about 40%.

If "dry ejaculation" occurs after limited RLND it is often due to true retrograde ejaculation.

After limited RLND, sympathico-mimetic drugs may reverse "dry ejaculation" in 50 to 70% of patients. Those with true retrograde ejaculation and normal serum FSH can thus be offered the chance of achieving fatherhood during treatment with sympathico-mimetics.

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The Authors

Sophie D. Fosså, MD, Consultant in Radiotherapy and Medical Oncology, General Department, Norwegian Radium Hospital.

S. Ous, MD, Consultant Urologist, Surgical Department.

T. Åbyholm, MD, PhD, Consultant Gynaecologist, Aker Hospital.

M. Loeb, MSc, Statistician, Norwegian Radium Hospital.

Requests for reprints to: S. D. Fosså, General Department, Norwegian Radium Hospital, Montebello, Oslo 3, Norway.

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Post-treatment Fertility in Patients with Testicular Cancer.

II. Influence of Cis-platin-based Combination Chemotherapy and of Retroperitoneal Surgery on Hormone and Sperm Cell Production

SOPHIE D. FOSSÅ, S. OUS, T. ÅBYHOLM, N. NORMAN and M. LOEB

General and Surgical Departments, Norwegian Radium Hospital; Gynaecological Department, Rikshospitalet; Hormone Laboratory, Aker Hospital, Oslo, Norway

Summary—Active sperm production was observed in 20 of 35 patients with testicular cancer 1 year after discontinuation of all treatment (retroperitoneal surgery only: 13; cis-platin-based chemotherapy (CVB) ± other treatment: 22). The percentage of patients who regained spermatogenesis increased slightly after a further 1 to 2 years. Fourteen patients (of 121 under observation) impregnated their wives (after retroperitoneal surgery: 9; after CVB ± other therapy: 5). The individual serum FSH values correlated significantly with the results of sperm analysis: an FSH value $\geqslant 20$ iu/l indicated azoospermia in 8 of 12 patients, whereas only 5 of 30 patients with FSH levels $\leqslant 12$ iu/l were azoospermic. Serum testosterone and pituitary serum LH were virtually unaffected by the treatment.

In conclusion, 1 to 3 years after cis-platin-based multi-modality treatment for testicular cancer, 50 to 60% of patients have active spermatogenesis and fatherhood can be achieved by a significant number of them.

A separate report dealt with disturbances of ejaculatory potency in patients with testicular cancer who had undergone retroperitoneal lymph node dissection (RLND) (Fosså *et al.*, 1985).

The present communication summarises our observations on hormone production and spermatogenesis ("fertility evaluation") after cis-platin-based combination chemotherapy and after retroperitoneal surgery only.

Patients and Methods

One hundred and twenty-one patients with testicular cancer (non-seminoma all stages: 103 patients; seminoma >stage IIB (Peckham *et al.*, 1981): 18 patients) underwent treatment as previously outlined (Table 1) (Fosså *et al.*, 1984). In 31 patients surgery was the only therapy. Ninety patients received three (40) or four (50) cycles of CVB (cis-platin, vinblastine, bleomycin) with or without other cystostatic drugs. Other cytostatic treatment (given after four cycles of CVB) included

Table 1 Treatment

Treatment		*Number of patients*
RLND* only		31
CVB** only		2
CVB + RLND		49
CVB + other cytotoxic treatment		39
CVB + other cytostatics ± RLND	12	
CVB + irradiation ± RLND	18	
CVB + cytostatics + irradiation	9	
Total		121

* RLND: retroperitoneal lymph node dissection.
** CVB: cis-platinum, vinblastine, bleomycin.

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cyclophosphamide, adriamycin, vincristine, actinomycin D, VP-16 and ifosfamide. Eighteen patients received abdominal irradiation after chemotherapy + retroperitoneal lymph node dissection (RLND) (total dose 40-50 Gy).

The patients were without evidence of disease at the time of post-treatment fertility evaluation, which was done at intervals of 1 year starting 12 months after discontinuation of treatment. In 39 patients sperm analysis was also done after orchiectomy before further treatment.

At least one post-treatment sperm analysis was done in 56 patients (total: 68 sperm analyses). In 34 patients sperm analysis was performed on the patient's ejaculate. In 22 patients with "dry ejaculate" or with a very small ejaculate (< 1 ml) the post-masturbation urine was analysed for the presence of sperm cells. In general, semen was obtained by masturbation after at least 3 days' sexual abstinence.

For the present study the semen was evaluated on the basis of number of sperm cells/ml, motility index (percentage of motile sperm cells × motility grade 0-4), and percentage of morphologically abnormal sperm cells.

Classification was as follows:

Azoospermia: no sperm cells.

Highly impaired spermatogenesis (HIS): number of sperm cells/ml < 10 million and/or motility index < 20 and/or percentage of abnormal sperm cells > 80.

Normospermia: normal sperm cells.

The motility index and percentage of abnormal sperm cells were not evaluated for the sperm cells found in the post-masturbation urine sample. If sperm cells were present in the urine, this finding was always classified as HIS.

At the time of sperm analysis the serum was analysed for LH, FSH and testosterone (Fosså *et al.*, 1980). Serum hormone analysis was also carried out on the 65 patients in whom sperm analysis was not performed.

Statistics Student's t-test and the χ^2 test were used in the statistical analysis. A P-value < 0.05 indicated statistically significant differences.

Results

Pre-treatment hormone and sperm analysis

The mean serum LH was moderately elevated owing to the occurrence of cross-reacting human choriogonadotrophin (HCG) in patients with metastatic testicular cancer (Table 2). The mean serum FSH and testosterone were within the normal range, although most individual testosterone values fell within the lower half of the normal range.

Seven patients were azoospermic, 17 had HIS and normospermia was observed in 15 (Table 3). A poor result of pre-treatment sperm analysis (azoospermia, HIS) did not exclude the possibility of subsequent normospermia and impregnation (Table 3).

Post-treatment hormone and sperm analysis

If all types of treatment were combined, the findings indicated that serum LH and testosterone remained virtually unchanged after treatment (apart from LH normalisation due to effective treatment of HCG-producing metastases) (Table 2). Serum FSH was increased significantly ($P < 0.05$) 1 year after treatment, with a tendency to gradual reduction during the following 2 years. We therefore analysed the serum FSH changes separately for the different types of treatment (Table 4). Retroperitoneal surgery *per se* did not have a significant influence on serum FSH. However, 1 year after CVB (± RLND) the mean serum FSH was significantly elevated. Three years after CVB treatment, 5 of 10 patients still had increased FSH values. In 4 of them FSH values between 12 and 20 iu/l were found.

The 1-year increase in serum FSH was more pronounced in patients in whom CVB chemotherapy was combined with other cytotoxic treatment (other cytostatic drugs and/or radiotherapy). In these patients the subsequent decrease in mean FSH was less distinct, especially if they had received combination chemotherapy (in addition to CVB) in large total doses and/or during several months.

Table 2 Mean Serum Hormone Levels* Before and After Treatment for Testicular Cancer (all treatment modalities)

	Before treatment	*After treatment*		
		1 year	*2 years*	*3 years*
LH (iu/l)	12.9 (44)	8.2 (96)	8.9 (57)	8.4 (32)
FSH (iu/l)	6.2 (45)	18.2 (95)	14.4 (60)	15.5 (33)
Testosterone (nmol/l)	16.9 (48)	17.8 (94)	17.9 (57)	20.4 (31)

* Normal range: LH: 2-12 iu/l. FSH: 2-12 iu/l. Testosterone: 12-40 nmol/l.

( ): number of patients analysed.

Table 3 Relation Between Pre- and Post-treatment Fertility

Sperm analysis	*Total*	*Azoospermia*	*After treatment*			
			*HIS**	*Normospermia*	*Unknown*	*Impregnation*
Before treatment						
Azoospermia	7	1	3	1	2	0
HIS*	17	3	6	1	7	5
Normospermia	15	3	3	6	3	4
Total	39	7	12	8	12	9
Impregnation		2	4	6	2	14

* HIS: highly impaired spermatogenesis.

Table 4 Mean Serum FSH (iu/l) Before and After Treatment of Testicular Cancer

Treatment	*Before treatment*	*After treatment*		
		1 year	*2 years*	*3 years*
RLND	7.2 (13)	10.2 (26)	10.8 (15)	9.1 (11)
CVB ± RLND	6.0 (22)	17.7 (42)	13.0 (22)	13.3 (10)
CVB + other cytotoxic treatment	5.1 (10)	26.7 (27)	15.8 (23)	23.2 (12)

( ): number of patients.

Table 5 Serum FSH and Post-treatment Sperm Analysis

FSH (iu/l)	*Azoospermia*	*HIS**	*Normospermia*	*Total*
⩽12	5	10	15	30
13-19	7	14	2	23
⩾20	8	4	0	12
Total	20	28	17	65

* HIS: highly impaired spermatogenesis.

Table 6 Sperm Analysis After Combination Chemotherapy Treatment for Testicular Cancer

Treatment	*After treatment*				
	Azoospermia	*HIS**	*Normospermia*	*Total*	*Impregnation*
RLND only:					
1 year	2	3	8	13	9
2-3 years	0	6	5	11	
CVB ± RLND:					
1 year	6	6	2	14	3
2-3 years	4	5	2	11	
CVB + other cytotoxic treatment ± RLND:					
1 year	7	1	0	8	2
2-3 years	7	3	1	11	
Subtotal:					
1 year	15	10	10	35	
2-3 years	11	14	8	33	
Total	26	24 (12)°	18	68	14

* HIS: highly impaired spermatogenesis.
( )°: number of sperm analyses performed in post-masturbation urine.

There was a significant correlation ($P<0.005$) between the individual serum FSH values and the results of simultaneous post-treatment sperm analysis (Table 5). A serum FSH level below 20 iu/l indicated active spermatogenesis (normospermia or HIS) with a high degree of accuracy, whereas FSH levels above 20 iu/l in 8 of 12 patients correlated with azoospermia.

Table 6 summarises the results of post-treatment sperm analyses and the frequency of impregnations within each therapeutic group. The majority of normospermic patients were found within the group treated with surgery only. One year after CVB 8 of 14 patients had regained active spermatogenesis, though HIS was the most frequent finding. Completely lacking or highly impaired spermatogenesis was found most frequently in patients who had undergone combined cytotoxic treatment, but even in this group a recovery of sperm production was noticeable in some patients.

In summary, 20 of 35 patients (57%) had sperm production 1 year after discontinuation of treatment. After 2 to 3 years, spermatogenesis was demonstrated in 22 of 33 men (67%).

Impregnation was most often reported by patients treated with RLND only. However, 5 men became fathers after cytostatic treatment: 3 after 3 to 4 cycles of CVB + retroperitoneal surgery and 2 after combined cytotoxic treatment ± RLND.

Discussion

We chose a lower limit of 10 million/ml for normospermia in this study. As our sperm evaluation also included a motility index and counting of abnormal forms, our normospermia group comprised individuals with a realistic possibility of achieving impregnation.

There was a significant inverse correlation between serum FSH and the result of sperm analysis. FSH is normally controlled by a negative feedback from the germinal epithelium in the testes, the hormonal messenger being the polypeptide inhibin (Setchell *et al.*, 1977). Serum FSH mirrors spermatogenesis to a high degree and gives information about sperm cell production even in patients in whom sperm analysis is not possible. From the present analysis it is also clear that only serum FSH (and spermatogenesis) are significantly affected by modern cis-platin-based chemotherapy. Serum testosterone and serum LH remain unchanged during treatment (apart from changes due to cross-reacting HCG). These observations confirm previous results from our institution and from other laboratories (Fosså *et al.*, 1980; Berthelsen *et al.*, 1983).

Only 20 to 35% of patients with testicular tumours are normospermic after orchiectomy before further treatment (Weissbach *et al.*, 1980; Berthelsen and Skakkebæk, 1983; Chiou *et al.*, 1984; Fosså *et al.*, 1985). The reason may be a primary dysgenesis in the remaining testis, HCG and oestradiol elevation due to tumour activity, or possibly the influence of stress in these young men who have a newly diagnosed malignant disease. Finally, a single sperm analysis may not always mirror the patient's basic fertility. Patients with reduced quantity or quality of sperm cells at the time of diagnosis of testicular cancer may hope for an improvement in spermatogenesis. Indeed, recovery from initial azoospermia was observed in 4 of 7 patients during follow-up. In addition, one of 17 patients with HIS became normospermic and 5 patients with initial HIS subsequently fathered a child. Our observations thus clearly indicate that the poor semen quality and/or quantity in the pre-treatment situation in patients with testicular cancer is a transient phenomenon in at least half of them.

There have been a few observations on restored fertility after modern cis-platin-based chemotherapy (Drasga *et al.*, 1983; Chiou *et al.*, 1984). Drasga *et al.* (1983) reported on 46% normospermic patients 2 to 3 years after completion of cis-platin-based chemotherapy. Eight of 25 patients fathered a child. The mean serum FSH reached a maximum after 1 year, with a gradual decrease to normal in 46% of the patients after 2 years. Chiou *et al.* (1984) described the recovery of fertility in 67% of patients examined 18 months or more after CVB treatment. Our results clearly confirm these observations. One year after completion of CVB, 8 of 14 patients showed signs of active spermatogenesis, with a slight increase in this percentage during the following 2 years. Contrary to the claims of Drasga *et al.* (1983), our observations indicate that a combination with other cytotoxic treatment (abdominal irradiation, especially long-term chemotherapy with other cytostatic drugs) decreases the possibility of recovery of post-treatment spermatogenesis. However, even in this group of patients with combined cytotoxic treatment, fatherhood was observed if the dose of adriamycin and cyclophosphamide was relatively low.

The fact that active spermatogenesis was found 1 to 3 years after CVB in a substantial percentage of patients is in clear contrast to previous observations in patients with testicular cancer treated by other types of combination chemotherapy. A previous report demonstrated azoospermia and elevated serum FSH in all 10 patients examined 1 to 3 years after long-lasting combination chemotherapy with adriamycin, cyclosphosphamide, actinomycin D, vincristine and medroxy-progesterone acetate (Fosså *et al.*, 1979). Thus modern CVB treatment is not only the most effective therapy in metastatic testicular cancer, but it also allows spermatogenesis to recover. Subsequent fertility is possible in at least 40% of patients.

After treatment for testicular cancer a normal or slightly elevated (<20 iu/l) serum FSH reflects active spermatogenesis at a high degree of probability. Serum testosterone and LH are not affected by modern cis-platin-based chemotherapy.

The infertility and hypofertility demonstrated by a single sperm analysis in an individual patient with testicular cancer should not be considered as permanent and irreversible. Normospermia and even fatherhood can be observed in orchiectomised patients with azoospermia or highly impaired spermatogenesis in a single sperm analysis before or after treatment.

One to 3 years after discontinuation of cis-platin-based chemotherapy, at least 50% of patients have active spermatogenesis. Avoidance of long-lasting combination chemotherapy and radiotherapy may help to preserve fertility.

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The Authors

Sophie D. Fosså, MD, Consultant in Radiotherapy and Medical Oncology, General Department, Norwegian Radium Hospital.

S. Ous, MD, Consultant Urologist, Surgical Department, Norwegian Radium Hospital.

T. Åbyholm, MD, PhD, Consultant Gynaecologist, Rikshospitalet.

N. Norman, FRCP(C), Head of Hormone Laboratory, Aker Hospital.

M. Loeb, MSc, Statistician, Norwegian Radium Hospital.

Requests for reprints to: S. D. Fosså, General Department, Norwegian Radium Hospital, Montebello, Oslo 3, Norway.

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Vasography, its Indications and Complications

S. R. PAYNE, J. P. PRYOR and C. M. PARKS

St Peter's Hospital and Institute of Urology, London

Summary—A retrospective study was undertaken of the results of vasography in 440 male partners of infertile marriages who had undergone scrotal exploration and in a group of 42 men with a variety of genital tract disorders. Abnormalities were observed in 10% of 265 azoospermic men and in 4% of 175 other men with infertility. There was no evidence that vasography caused damage to the vas deferens and no oligozoospermic man became azoospermic. A high incidence radiological of abnormalities was seen in haemospermia but the incidence of abnormalities in selected men with ejaculatory problems or testicular pain was low.

The indications for vasography and its diagnostic efficacy are unclear both in the investigation of male infertility and of genital tract disorders that have defied conventional investigation. Vasography has been deprecated as an investigation in the management of male infertility due to its supposed deleterious effects on the vasal and epididymal ductal epithelium (Wagenknecht, 1982). This may be due either to infection or to the harmful effects of hydrophobic contrast media on the ductal epithelium, as has been shown experimentally in rats (Wagenknecht *et al.*, 1982). This retrospective study was undertaken to assess the benefits and complications of vasography.

Patients and Methods

Four hundred and eighty-two men underwent vasography during the years 1975 to 1983, 265 for obstructive azoospermia, 175 for infertility (usually severe oligozoospermia but in some men having a varicocele ligated), and a miscellaneous group of 42 patients. This latter group comprised 26 men with haemospermia, 10 with ejaculatory problems and 4 with undiagnosed testicular or epididymal pain.

Vasography was performed under general anaesthesia and usually at the time of scrotal exploration. The vas was isolated on each side with a 2/0 chromic catgut sling and injected directly with 1 to 2 ml Urografin 325 58% or Hypaque 45% via a 25G needle from a 10 ml syringe. Imaging was performed using a standard 24 × 30 cm fast film/screen combination X-ray cassette which was placed under a radiolucent mattress. A collimated X-ray beam centred 5 cm above the symphysis pubis was used to expose the cassette, using an exposure of 100 mA at 53 Kvp for between 0.2 and 0.5 s; respiration was suspended for the longer exposures to stop film blur. During the years 1975 to 1977 an antegrade injection of contrast towards the epididymis was performed and imaged on a "kidney film". The processed film was viewed in theatre and any surgically treatable lesion dealt with during the same operating session.

Repeated semen analyses were performed on fresh specimens before and after testicular exploration and analysed using the World Health Organization criteria (Belsey *et al.*, 1980). Infertile men having vasography were divided into groups (depending on whether their pre-operative sperm concentrations were zero, less than 1 million, less than 10 million or less than 100 million per ml), and changes occurring after vasography were noted.

Results

A normal vasogram (Fig.) was seen in 427 men. Radiological abnormalities were reported in 55

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

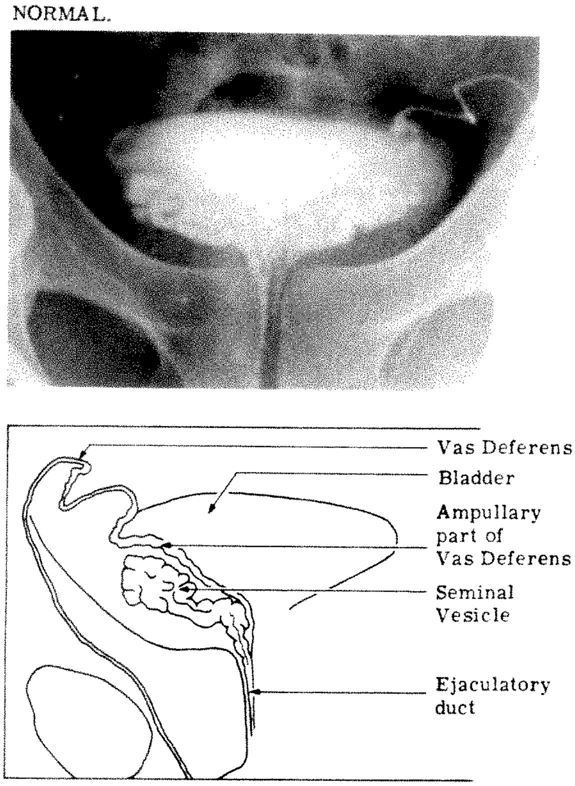

Fig. A normal vasogram showing the anatomy of the seminal tract. There is uniformity of the vasal diameter with symmetrical seminal vesicles which empty into an undilated ejaculatory duct. Contrast can be seen in the prostatic urethra and a small amount has passed retrogradely up into the bladder. There has been uniformity of filling of the system and there is no extravasation at any point.

patients (11.7%) and were most common in the miscellaneous group where abnormalities were seen in 22 patients (52%). Abnormalities were seen in 26 azoospermic patients (10%) and only 7 (4%) of the other infertile men (Table 1).

Abrupt vasal blocks with proximal dilatation were seen in 10 patients; close to the testicle in one, in the inguinal region in five and deep to the internal ring in four. Vesicular blocks at the level of the seminal vesicle or vesicular or ejaculatory ducts were seen in six men. Two men had blocks at the level of the ejaculatory duct and the remaining four had dilated seminal vesicles. Inflammatory changes were the most frequent abnormality, being seen in 30 men; all of these men had either ectasia or dilatation of part of the seminal tract without obstruction. Congenital defects of the ejaculatory system were seen in five men, occurring together with abnormalities of the upper urinary tracts, cysts of embryonic duct remnants, diverticula of the vasa and anorectal anomalies.

In azoospermia, recognition of a vasographic abnormality precipitated exploration and vasovasostomy in those men with blocks in the scrotal and inguinal vas and transurethral incision of dilated vesicular systems. Contrast visualisation of the portion of the vas closest to the epididymis was, however, found to be a poor assessor of the proximal vasal anatomy and was abandoned after 1977.

In oligozoospermia it is important to diagnose the underlying pathology, since patients with inflammatory changes in the seminal vesicle responded to antibiotic therapy. Men with a round cell infiltrate in their testicular biopsy but otherwise normal histology and no obstructing lesion received steroid therapy.

One hundred and fifty-four men in whom no reconstructive surgery was performed and who received no drug therapy before the post-operative semen analyses were studied to see if there were any ill effects of vasography. Sperm concentrations remained unaltered in 96 members of this group; there was an increase in concentration in 29 and a decrease in 29 men. A sustained decrease in sperm concentration was seen in only 12 men 3 months post-operatively, the others all reattaining their pre-operative levels. No oligozoospermic man was rendered azoospermic as a consequence of this procedure.

There was a high incidence of abnormalities (73%) in the 26 men with haemospermia, but only two abnormalities (inflammatory change in one and a filling defect in another) were seen in the 10 men with ejaculatory problems and inflammatory

Table 1 Summary of Radiological Abnormalities Seen at Vasography

Presentation	*Vesicular block*	*Vasal block*	*Inflammatory change*	*Filling defects*	*Congenital abnormalities*
Azoospermia	5	8	9	1	3
Oligozoospermia	1	2	3	0	1
Miscellaneous	0	0	18	3	1
Total	6	10	30	4	5

change was seen only once in the four men presenting with epididymal or testicular pain.

Discussion

Contrast visualisation of the seminal tracts has been used since the beginning of the present century (Bellfield, 1913) but has never enjoyed popularity except in the hands of enthusiasts (Boreau, 1974). There is no doubt that vasography is an invasive investigation and its application has therefore been limited by its diagnostic capabilities together with the potentially deleterious effects of the procedure on vasal and epididymal patency.

Testicular exploration and biopsy have been shown to be a justifiable investigation in the management of the infertile male who has a normal serum FSH level and normal testicular size (Pryor *et al.*, 1978). Vasography can easily be performed at testicular exploration and can define coexistent vasal or seminal vesicular blocks in addition to abnormalities of the epididymes. Coexistence of inflammatory lesions causing both epididymal and vasal lesions are particularly amenable to surgical correction (Hendry, 1981). Short vasal blocks, if situated in the proximal tract, may be dealt with by excision and vasovasostomy, and vesicular lesions by transurethral incision of the ectatic ducts (Vicente *et al.*, 1983). This may be facilitated by injecting methylene blue antegradely into the dilated ductal system at vasography.

The high incidence of radiological abnormalities seen in patients with haemospermia justifies the use of vasography together with cystourethrography in patients in whom the pathological aetiology cannot be diagnosed by culture of the urine, semen or prostatic fluid (Fletcher *et al.*, 1981). Radiologically demonstrated distortion of the seminal vesicles and persistent haemospermia require excision of the seminal vesicle to exclude malignancy, although pathological rarities such as amyloidosis may present in this way. Vasography has a low diagnostic yield in such nebulous conditions as perineal and testicular pain and ejaculatory disorders. However, one patient with ejaculatory pain and low semen volumes was improved by incision of his dilated and obstructed seminal vesicle.

Cannulation of the vas is undoubtedly more traumatic than direct needle puncture, the latter having little detrimental effect on vasal architecture at a microscopic level (Wagenknecht *et al.*, 1982). The use of high concentration hydrophobic contrast media does, however, appear to cause vasal scarring in a rat vas model, although the applicability of this to man is unclear. We have not found that the use of either 58% Urografin or 45% Hypaque does cause vasal occlusion in man and it does not appear to alter the semen quality significantly. Certainly other factors such as anaesthesia, debilitation following surgery and seasonal influences (Tjoa *et al.*, 1982) may well have contributed to the decreased semen concentrations observed in 8% of our infertile men immediately after vasography.

We therefore conclude that vasography is a safe and informative investigation essential in the full evaluation of male infertility and helpful in the evaluation of the underlying pathology of recalcitrant haemospermia.

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The Authors

S. R. Payne, FRCS, Lecturer.
J. P. Pryor, MS, FRCS, Consultant Urologist.
C. M. Parks, FRCR, Consultant Radiologist.

Requests for reprints to: S. R. Payne, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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The Clinical Presentation of *Chlamydia trachomatis* in a Urological Practice

J. B. F. GRANT, P. J. C. BROOMAN, S. D. CHOWDHURY, P. SEQUEIRA and N. J. BLACKLOCK

Departments of Urology and Serology, University Hospital of South Manchester, Manchester

Summary—Fifty-nine men with *Chlamydia trachomatis* (CT) infection have been studied. Epididymitis was the most common presentation (26) compared with urethritis (8) and prostatitis (9). Only 13 patients gave a history of a urethral discharge. Fifteen of 21 female consorts screened were CT positive and 13 of these were asymptomatic. This demonstrates the major aetiological role of CT in lower genitourinary infection and indicates the importance of screening and treating consorts.

There is increasing evidence of the frequency of *Chlamydia trachomatis* in lower urinary tract infection in men. This study reviews a series of men in whom CT was detected by either positive culture or raised antibody titres.

Patients and Methods

Since 1980, male patients presenting with symptoms of lower genitourinary infection have been investigated as outlined in Table 1. Bacterial culture was performed on blood and chocolate agar plates and an additional swab was sent in Stuart's transport medium. CT culture was undertaken in McCoy cell lines. Antibodies to CT were detected by microimmunofluorescent techniques against genital pool and LGV pool antigens. Where possible the female consorts of the patients were traced and screened for CT by taking urethral and cervical swabs for CT culture and by assessing antibody titres. The skin test was a modified Frei test using LGV 2 antigen.

Results

CT infection was detected in 59 men whose ages ranged from 17 to 70 years (mean 33.1 years). They were detected by positive culture in 22, antibody titres of 1:512 or over in 23 and antibody titres of 1:128 in 16 men. The symptoms with which they presented and the clinical diagnoses made are shown in Tables 2 and 3.

Epididymitis

The age distribution of the 26 patients is shown in the Figure; nine patients were culture positive for CT and this was associated with antibody titres of 1:512 (5) and 1:128 (2). Of the 17 patients who were culture negative, 12 had antibody titres of 1:512 and 5 had titres of 1:128. In five patients under the age of 35 years associated infections were identified: *N. gonorrhoea* (2), *N. gonorrhoea* and cytomegalovirus (1), cytomegalovirus (1) and haemolytic streptococcus (1). One of the four patients over the age of 35 years was culture positive for CT; two, however, also had urinary tract infections (*E. coli*; enterococcus) and one also had bacterial prostatitis (*E. coli*).

"Non-bacterial" Prostatitis

Three of the nine patients were culture positive for CT with antibody titres of 1:512, whilst those who were culture negative had antibody titres of 1:512 (3) or 1:128 (3).

Urethritis

All eight patients presented with urethral discharge and all were culture positive for CT.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Table 1 Method of Investigating Men with Lower Genitourinary Infection

	Tests performed					
Specimens collected	*Microscopy*	*pH*	*Bacterial culture*	*CT culture*	*Bacterial antibodies*	*CT antibodies*
VB1	√		√			
VB2	√		√			
Urethral swab				√		
Prostatic massage to produce EPS	√	√	√	√		
Post-massage urethral swab				√		
VB3	√		√			
Clotted blood					√	√
Skin test						

Table 2 Presenting symptoms

Painful scrotal swelling	26
Dysuria	22
Haematuria	18
Discharge	13
Frequency	10
Haemospermia	1
Swollen knee	1

Table 3 Clinical Diagnosis at Presentation

Epididymitis	26
"Non-bacterial" prostatitis	9
Urethritis	8
Infertility	4
"Pain"	6
Penile warts	3
Consort of patient with CT	3

Infertility

One of the two patients who presented with primary infertility had severe oligozoospermia; the other had a normal sperm count but a low percentage of normally motile sperms. Two patients presented with secondary infertility; one had oligozoospermia and a varicocele and the other had oligozoospermia with a low percentage of normally motile sperms.

Penile Warts

All three patients with warts were otherwise asymptomatic when they presented, although one gave a history of genital herpes.

Consorts of Patients with CT

Three asymptomatic men with CT entered the study as the result of being screened as the male consorts of symptomatic female patients in whom CT was detected.

It was possible to screen 21 female consorts of men in this series. Fifteen were positive for CT and 13 of these were asymptomatic.

Discussion

The development of techniques to culture CT in McCoy cell culture and the microimmunofluorescent methods for measuring circulating antibody titres have made it possible to detect CT infections. As a result of the use of these techniques the prevalence of this infection is now realised to be widespread. The importance of CT as a cause of non-gonococcal urethritis (NGU) is well established (Dunlop *et al.*, 1972; Oriel *et al.*, 1972; Alani *et al.*, 1977). Most patients present to sexually transmitted disease clinics. The referral pattern to a department of urology is clearly different, as the spectrum of cases we have described illustrates. Urethritis was noted in only 8 cases (13%) and only 13 of the 59 patients admitted to a urethral discharge in the past. A larger number of patients (19) had passed blood urethrally, whether at the time of micturition or of ejaculation, and this no doubt prompted their referral to our clinic.

Epididymitis was by far the most common clinical presentation. The association between epididymitis and CT was first suggested by Heap (1975). The subsequent description of more cases and the isolation of CT from the fluid aspirated from the epididymis confirmed its role as a causative agent (Harnisch *et al.*, 1977; Berger *et al.*, 1978). We have

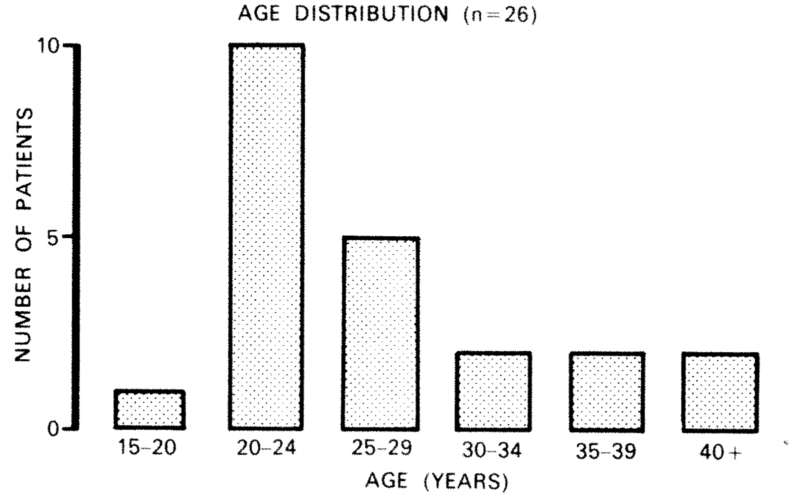

Fig. Age distribution of patients with epididymitis in whom CT was detected.

confirmed their observations that most of these patients are under the age of 35 years and that in this age group CT is the most common infective agent isolated. In the few cases where another infective agent is isolated this is also frequently sexually transmissible. By contrast, patients over the age of 45 years who develop epididymitis usually have either a bacterial prostatitis or bladder outflow obstruction with an associated urinary tract infection.

These observations have important implications in the management of patients with epididymitis. In the absence of adequate microbiological studies, inappropriate antibiotic therapy may be prescribed which will fail to eradicate CT. This can be successfully achieved with an adequate course of either tetracylines or erythromycin (Oriel and Ridgway, 1982). In addition, the importance of screening the consorts of all patients with CT infections is only fully realised when it is considered as a possible causative agent.

We were able to screen only 21 consorts of the 59 patients in this series but 71% of these were positive for CT, a figure comparable with that reported in other studies (Oriel *et al.*, 1972; Paavonen *et al.*, 1978). Most of these patients are asymptomatic and would, therefore, not seek medical attention unless encouraged to attend the clinic. The great number of asymptomatic patients with CT infection who continue to disseminate it in the absence of treatment clearly contributes to the rising prevalence of this infection.

The cervix is the site from which CT is most readily isolated in consorts of symptomatic male patients but the infection may also affect the female urethra (Woolfitt and Watt, 1977; Paavonen, 1979). In a prospective study, Staam *et al.* (1980) confirmed these findings by isolating CT in three asymptomatic control women but in all there was a significant pyuria, which was defined as 8 or more leucocytes per cubic millilitre in fractional urine samples. Furthermore, they demonstrated the importance of this type of infection in symptomatic women suffering from the urethral syndrome by confirming CT infection in 10 of the 16 patients with a sterile pyuria on routine bacterial culture. CT infection should, therefore, be considered in women who present with the urethral syndrome or recurrent cystitis, especially when a sterile pyuria is found. The site of the infection in women can be identified only if fractional urines (VB1, VB2) are collected.

Prostatitis can be diagnosed if fractional urines and EPS are examined microbiologically (Meares and Stamey, 1968). In many cases bacterial culture identifies the causative organism but 50% of patients are culture negative—"non-bacterial" prostatitis (Brooman, unpublished data). We have isolated CT in three such cases and found high antibody titres to CT in a further six. These findings provide evidence to implicate CT in the pathogenesis of prostatitis and contrast with the conclusions of Mardh *et al.* (1978) that CT plays only a minor role, if any, in prostatitis.

The role of CT in male infertility is not yet clear but remains under active investigation. Genitourinary infection has been shown to produce a variety of effects, reducing the potential fertility of the male partner (Caldamone and Lockett, 1978). As the evidence accumulates to implicate CT in prostatitis and a common cause of epididymitis in young men, it seems probable that in some patients it will contribute to their infertility. Patients with CT infections may, therefore, present regularly to a urogical department in a variety of ways. It is hoped that awareness of its major aetiological role in lower genitourinary infections will result not only in an increase in its diagnosis, but also in the effective treatment of those patients and consorts.

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The Authors

J. B. F. Grant, MD, FRCS, Urological Senior Registrar.
P. J. C. Brooman, FRCS, Urological Senior Registrar.
S. D. Chowdhury, FRCS, Senior Lecturer in Urology and Honorary Consultant.
P. Sequeira, MB, BS, Director of Central Serology Laboratory.
N. J. Blacklock, FRCS, Professor of Urology.

Requests for reprints to: J. B. F. Grant, Department of Urology, Withington Hospital, Nell Lane, West Didsbury, Manchester M20 8LR.

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Urinary Infection in Adult Men: a Laboratory Perspective

MINA CLARKE, LINDA PEAD and ROSALIND MASKELL

Public Health Laboratory, St Mary's Hospital, Portsmouth

Summary—During a 10-week period all mid-stream urine specimens from males aged 15 years and upwards, excluding hospital in-patients, with symptoms suggesting urinary tract infection were examined by techniques capable of detecting aerobes and fastidious organisms. Five hundred and eighty-five such specimens were received; 85% were sent by general practitioners and 182 were from men aged less than 45 years, indicating that urinary symptoms are commoner in young men than is usually believed and that diagnosis and treatment are usually undertaken by general practitioners. One hundred and seventy-nine specimens yielded aerobic pathogens and 140 yielded fastidious organisms; 70% of the former and 33% of the latter showed pyuria. Only 12% of the 196 specimens showing pyuria yielded a negative culture. The possibility of prostatic infection and its relevance to treatment are discussed. Some post-treatment data are presented.

Many years of experience of examining urine specimens from adult male patients has left us with the strong impression that dysuria and frequency are commoner than is widely supposed in such patients, that agents such as ampicillin and nitrofurantoin, which do not penetrate prostatic tissue (*Lancet*, 1983), are seldom effective in eradicating infection, and that overnight aerobic culture detects a pathogen in only a minority of men with symptoms, even in many of those with pyuria.

The role of the commensal anaerobes and fastidious organisms of the female genital and urinary tracts in invading adjacent tissues is increasingly recognised, and there have been a few reports of such organisms causing definite clinical infection of the bladder (Abercrombie *et al.*, 1978) and of the prostate (Goetz and Craig, 1982) in adult men.

In order to investigate the frequency with which fastidious organisms could be isolated from the urine of men with symptoms when conventional aerobic culture was negative, we studied urine specimens received in our laboratory during a 10-week period in the autumn of 1983.

Patients and Methods

All mid-stream urine (MSU) specimens received from male patients of 15 years and upwards outside hospital, with a request form indicating urinary symptoms or a diagnosis of urinary tract infection (UTI), prostatitis or epididymo-orchitis, were included in the study. Microscopy of uncentrifuged urine was performed by the inverted microscope method (Maskell, 1982); pyuria, for the purpose of this study of male patients, was defined as the presence of more than two leucocytes per field. Cysteine lactose electrolyte deficient (CLED) agar, chocolated blood agar (CBA), and blood agar (BA) plates were each inoculated with 0.005 ml urine using a standard loop. The CLED and CBA plates were incubated in an atmosphere containing 7% CO_2 and read at 18 and 48 h. The BA plate was incubated for 48 h in an anaerobic cabinet (Don Whitley Mk II); 20 µl of urine were also inoculated on to 1/6 of a serum assay agar plate seeded with *Bacillus subtilis* which was incubated overnight in air. All isolates were recorded and the results were classified in three categories: positive, in which recognised pathogens grew on all media overnight; fastidious, in which organisms grew on the CBA or

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BA plate and there was no growth on the CLED plate up to 48 h; and negative, in which there was either no growth on all media or a mixed growth of fewer than 10^6/l mixed Gram positive organisms (assumed to be commensal urethral flora) on all media. Isolates of accepted urinary pathogens were identified to species level, using standard methods for streptococci and staphylococci, and a 23 test multipoint inoculation system (Mast) for Gram negative organisms. Fastidious organisms were identified, when possible, to genus level by colonial characteristics, Gram film, and catalase and coagulase tests when appropriate. Antibiotic sensitivity testing, when indicated, was by a modified Stokes method (Pearson and Whitehead, 1974). All organisms were tested against nitrofurantoin, sulphonamide, amoxycillin, co-trimoxazole and tetracycline; Gram positive and fastidious isolates were also tested against erythromycin. Isosensitest agar (ISA) was used for aerobic isolates, and blood ISA "chocolated" at 56°C overnight for fastidious isolates. Clearing of bacterial growth on the *B. subtilis* plate was accepted as evidence of the presence of an antibacterial substance in the urine, suggesting that the patient was on treatment.

All reports of either aerobic or fastidious isolates were sent out with a suggestion that treatment, if still indicated clinically, should be with one of the agents which penetrate prostatic tissue (co-trimoxazole, a tetracycline such as doxycycline, or erythromycin stearate in the case of Gram positive isolates) in accordance with the sensitivity of the organism. The sensitivity of the one isolate of *Bacteroides* sp. to metronidazole was reported. However, we are not aware of any good evidence as to the prostatic concentration achieved with this agent. An attempt was made to monitor treatment and clinical progress of patients from whom fastidious organisms were isolated by sending a further request form with the report, asking for a follow-up specimen and details of any treatment given and persistence or disappearance of symptoms. No request was made for post-treatment specimens from patients with aerobic infection, but the results of such specimens, if received, were recorded.

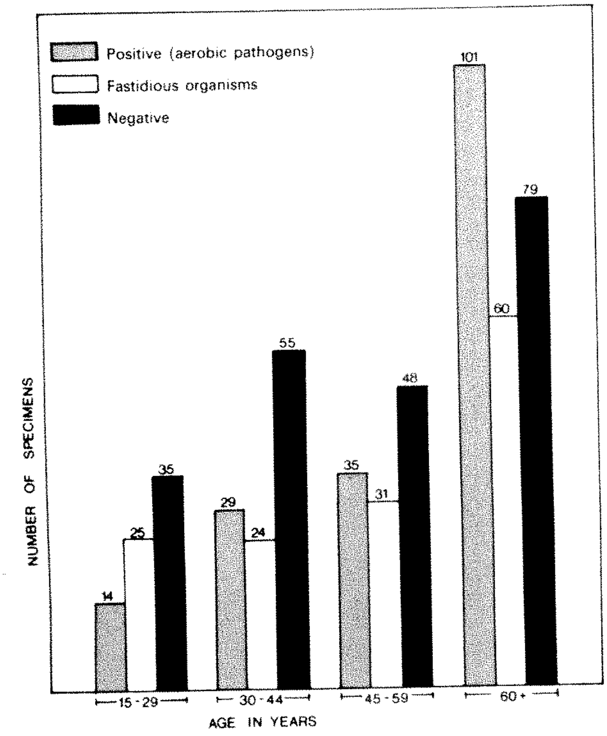

Fig. Age distribution and culture results of 536 MSU specimens.

Results

Five hundred and eighty-five specimens which fulfilled the criteria were received from 567 men during the 10-week study: 495 from general practitioners, 79 from various hospital out-patient departments, and 11 from the Department of Genito-urinary Medicine. Forty-nine specimens which yielded a negative culture showed evidence of antibacterial activity and were excluded from the analysis. The figure shows the age distribution and the culture results of the remaining 536. Pyuria was found in 126 (70%) of the 179 yielding a positive aerobic culture, in 46 (33%) of the 140 yielding fastidious organisms, and in 24 (11%) of the 217 negative specimens. Thus, of the 196 specimens with pyuria only 24 (12%) yielded a negative culture.

Table 1 summarises the organisms isolated from the positive specimens; 20 (11%) yielded mixed cultures of Gram negative and Gram positive organisms and 24 (14%) yielded Gram positive organisms only. The majority of the latter were isolated from the older patients.

Table 2 shows the fastidious organisms isolated. Table 3 shows the bacterial counts, both of aerobes and fastidious organisms, and relates them to age and to pyuria. Table 4 shows the antibacterial sensitivities.

An attempt was made to correlate particular symptoms as recorded on the request forms with culture findings, but as the requests were made by so many different doctors no conclusions were possible.

There were two groups of patients, however, in

Table 1 Organisms Isolated on All Media from 179 Patients (Positive Group)

Age in years	*E. coli*	*Proteus sp*	*Other Gram negative*	*Mixed Gram negative*	*Gram negative and Gram positive*	*Staph. aureus*	*Staph. epidermidis*	*Strep. faecalis*	*Group B streptococcus*	*Mixed Gram positive*†	*Total*
15-29	9	2	3	0	0	0	0	0	0	0	14
30-44	17	2	1	1	5	0	0	2	1	0	29
45-59	22	1	2	2	2	0	2	2	0	2	35
>59	42	12	15	4	13	2	4	7	0	2	101
Total	90	17	21	7	20	2	6	11	1	4	179

† Mixed cultures of streptococci and staphylococci.

Table 2 Fastidious Organisms Isolated from 140 Patients (Fastidious Organisms Group)

Age in years	*Corynebacterium sp*	*Fastidious streptococci*	*Lactobacillus sp*	*Moraxella sp*	*Bacteroides sp*	*Anaerobic Gram-positive cocci (not identified)*	*Mixed fastidious organisms*†	*Total*
15-29	11	1	1	0	0	1	11	25
30-44	8	5	1	0	1	0	9	24
45-59	15	8	0	0	0	0	8	31
>59	17	12	0	1	0	5	25	60
Total	51	26	2	1	1	6	53	140

† Mixed cultures of more than one fastidious species.

Table 3 Bacterial Counts and Pyuria in Positive and Fastidious Organism Groups

	$<10^7\,l^{-1}$		10^7-$10^8\,l^{-1}$		$>10^8\,l^{-1}$		*Total*	
Age in years	*Positive*	*Fastidious organism*	*Positive*	*Fastidious organism*	*Positive*	*Fastidious organism*	*Positive*	*Fastidious organism*
15-29	6(0)	17(3)	2(1)	3(1)	6(5)	5(2)	14(6)	25(6)
30-44	6(3)	19(2)	8(4)	5(1)	15(12)	0	29(19)	24(3)
45-59	5(1)	21(3)	5(4)	8(3)	25(23)	2(2)	35(28)	31(8)
>59	18(7)	35(13)	21(10)	18(9)	62(56)	7(7)	101(73)	60(29)
Total	35(11)	92(21)	36(19)	34(14)	108(96)	14(11)	179(126)	140(46)

Figures in brackets = number of specimens with pyuria.

Table 4 Percentage of Organisms Sensitive to Antibiotics Tested

	Nitrofurantoin	*Sulphonamide*	*Amoxycillin*	*Co-trimoxazole*	*Tetracycline*	*Erythromycin*
Aerobic organisms						
Gram negative	70	74	66	83	74	NT
Gram positive	100	44	76	72	56	72
Fastidious organisms	60	20	88	30	60	75

NT = Not tested.

whom there was a particularly high isolation rate—those who had had a recent prostatectomy and those undergoing radiotherapy for bladder malignancies. Table 5 shows the findings in these groups.

Table 5 Results from Post-Prostatectomy Patients and Patients Undergoing Radiotherapy

	Positive	*Fastidious*	*Negative*	*Total*
Post-prostatectomy	11(9)	12(10)	9(5)	32(24)
Radiotherapy	3(3)	3(3)	0	6(6)

Figures in brackets = number of specimens with pyuria.

Table 6 shows whether follow-up specimens were received from patients in the positive and fastidious organisms groups, and whether infection had disappeared after treatment. Insufficient information was given on request forms to enable us to draw any conclusions about length of treatment given or disappearance of symptoms.

Discussion

The number of adult men with urinary symptoms from whom we received specimens during the 10-week study was unexpectedly large. The fact that 85% presented to their general practitioners indicates that the great majority of such patients are seen and treated in general practice, not by hospital out-patient departments. The role of the diagnostic laboratory in diagnosis and guidance about treatment is therefore important.

Our results confirm the experience of many studies (*Lancet*, 1983) that overnight aerobic urine culture is positive in only a minority of patients—34% in our study. The use of methods designed to detect fastidious organisms was successful in a further 26%. These latter specimens yielded fastidious organisms only. The streptococci and staphylococci of the commensal flora of the distal urethra, which grow on CLED agar, were completely absent, making the explanation of contamination less likely. The fastidious organisms may have invaded the prostatic ducts or tissue, giving rise to symptoms in these patients; 33% of these specimens showed pyuria, compared with 70% of those yielding aerobic pathogens; only 14 (10%) were isolated in a count of 10^8/l compared with 108 (60%) of the aerobes. High counts of bacteria in the urine are indicative of multiplication in the bladder urine. It seems likely, therefore, that many of the patients with aerobic infection had either primary bladder infection, or possibly extension of infection from the prostate. Fastidious organisms are less likely to survive in the oxygen concentration of bladder urine (Leonhardt and Landes, 1963), and infection would probably remain confined to tissues below the bladder. Pyuria was found in 35 patients with counts of fastidious organisms of less than 10^8/l, indicating inflammation; the fact that it was not found in the majority suggests that inflammatory cells in the prostate may not always be shed into the urine. This situation has been demonstrated in other studies by the use of prostatic massage (Meares and Stamey, 1968). It is possible, of course, that other organisms responsible for inflammation were not detected; obligate anaerobes (many of which would not survive the inevitable delay in processing out-patient specimens and those received from general practice), *Chlamydia trachomatis* and ureaplasmas are possibilities. However, only 24 (12%) of the 196 specimens showing pyuria yielded a negative culture. We were surprised to receive only 11 specimens from the large Department of Genito-urinary Medicine (venereology) which we serve; 8 yielded negative cultures and none of these showed pyuria, suggesting that urethritis due to sexually transmitted pathogens was unlikely in these patients.

Fastidious organisms were isolated from patients of all ages and, unlike that of the aerobic

Table 6 Follow-up Specimens from Patients in Positive or Fastidious Groups

	No follow-up		*Sterile after treatment*		*Persistent infection after treatment*	
Age in years	*Positive*	*Fastidious*	*Positive*	*Fastidious*	*Positive*	*Fastidious*
15-29	8	17	5	5	1	3
30-44	13	13	15	6	2	5
45-59	13	17	17	12	5	2
>59	62	32	21	14	18	14
Total	96	79	57	37	26	24

pathogens, the isolation rate was similar in all age groups. Isolation from patients who had recently undergone prostatectomy was probably related to selection of such organisms by antibiotic therapy—reports of coryneform bacteria as nosocomial pathogens have been appearing in recent years (Young *et al.*, 1981; Finger *et al.*, 1983). Fastidious organisms could survive and multiply in the relatively anaerobic conditions obtaining in necrotic bladder tumours in patients undergoing radiotherapy. We isolate these organisms so often from such patients, both male and female, that we now incorporate additional media in our routine protocol for them. Perhaps the symptoms and inflammatory cells which are attributed to "post-radiation cystitis" could sometimes be due to infection with organisms not detected by routine culture methods.

It was disappointing that we were unable to draw any definite conclusion about treatment. It was clear, however, from the information we received with follow-up specimens that the agents we suggested were being used. We know that organisms, whether aerobic or fastidious, disappeared after appropriate treatment from 94 (65%) of the 144 patients from whom post-treatment specimens were received, treatment failure being higher in the older age groups. Failure may have been due to persisting pathological conditions of the urinary tract in some; in others the duration of treatment was inadequate to eradicate tissue infection (*Lancet*, 1983). The fact that no further specimens have been received 3 months after the end of the study from 175 (55%) of the 319 patients from whom organisms were isolated suggests that they may have been cured.

The limitations of a laboratory-based study such as this are obvious. They are to some extent outweighed by the large number of specimens which could be analysed in this way. Data about symptoms and treatment are inevitably inadequate and could only be obtained in a careful prospective clinical study. It is clear from our figures that any out-patient department would be unlikely to accumulate a sufficient number of patients for this purpose unless referral of patients in the acute phase was specifically sought from general practitioners. The logistic difficulties of this are well known. For the present, we shall continue to recommend 7 to 10 days' treatment of proven infection in male patients with agents which penetrate prostatic tissue, hoping to prevent chronic prostatitis due to inadequate treatment; to request further specimens for additional culture methods from patients with pyuria or symptoms unexplained by overnight culture on CLED agar; and to culture all specimens from patients undergoing radiotherapy by methods designed to detect fastidious organisms.

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The Authors

Mina Clarke, AIMLS, Senior Medical Laboratory Scientific Officer.
Linda Pead, AIMLS, Research Assistant.
Rosalind Maskell, MA, DM, Senior Medical Microbiologist.

Requests for reprints to: Rosalind Maskell, Public Health Laboratory, St Mary's Hospital, East Wing, Milton Road, Portsmouth PO3 6AQ.

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Prevention of Wound Infection Following Vasectomy

P. E. RANDALL, L. A. GANGULI, M. G. L. KEANEY and R. W. MARCUSON

Departments of Surgery and Microbiology, Hope Hospital, Salford

Summary—A prospective study on 90 patients undergoing vasectomy as day cases is reported. The use of a chlorhexidine gluconate bath or shower on day 1 and day 2 post-operatively reduced the wound infection rate from 37.8 to 6.7%. It is suggested, therefore, that this technique is an economical and successful way of reducing the incidence of infection in these patients.

There continues to be confusion in the literature concerning the risks of developing wound infection after vasectomy. The incidence is considered to be low by some workers (Esho *et al.*, 1973; Margaret Pyke Centre, 1973; Schmidt, 1975; Appel and Evans, 1980) but Blandy (1976, 1979) and Finkbeiner *et al.* (1977) consider infection to be common. More recently Sharma and Sadasukhi (1983) reported an infection rate of 5% in 200 cases.

Our own work (Randall *et al.*, 1983) revealed an infection rate of 32.9%. The majority of these infections were mild but there is a risk of complications. Two of our patients, with purulent discharge, required readmission to hospital and one developed septicaemia. Pryor *et al.* (1971) have described scrotal gangrene following vasectomy.

It has been shown (Ayliffe *et al.*, 1983; Leigh *et al.*, 1983; Randall *et al.*, 1983) that a single preoperative shower using chlorhexidine gluconate (Hibiscrub, ICI) reduces the skin flora significantly and yet does not affect the subsequent infection rate. We did not show any surgical factor contributing to the infection rate and, as the patients were arriving in theatre with a significant reduction in bacterial flora, we considered that wound infection following vasectomy was a secondary phenomenon occurring after the patient left hospital. Scrotal wounds are difficult to seal and bacterial invasion may follow abrasion by clothing.

We decided to study the value of additional postoperative showering with chlorhexidine gluconate in reducing wound infection.

Patients and Methods

Ninety patients were admitted as day cases to the same ward between January and June 1983. They were shaved on admission and before any other procedure was undertaken. All patients then had a scrotal swab taken in a standard manner, by rolling the swab several times against the area being sampled. All patients underwent a pre-operative shower with chlorhexidine gluconate. They were asked to pay particular attention to the scrotum and perineum. The shower was taken not more than 1 h before surgery. The patients were then randomly assigned to two groups. Group I consisted of 45 patients undergoing surgery who, after discharge, were advised to have salt baths after 24 h. This is the usual advice given to vasectomy patients and this group was considered to be the control. Group II consisted of 45 patients undergoing surgery who were discharged with 100 ml chlorhexidine gluconate, 50 ml to be used with either a bath or a shower on day 1 post-operatively and 50 ml on day 2. They were advised again to pay particular attention to the scrotum and perineum. The surgeon was not required to alter his choice of anaesthetic, skin preparation or surgical technique, as we have previously shown (Randall *et al.*, 1983) that these do not affect the subsequent infection rate.

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The patients were asked to return to the ward 7 days post-operatively and the wound was checked by one observer (PER). If the wound satisfied the criteria for infection, a wound swab was taken and cultured.

For the purpose of the study, the following definition of wound infection was used. A wound was considered to be infected if it was open and discharging either purulent or serous fluid. An erythematous wound was not considered infected, this being an inflammatory reaction to catgut skin sutures.

The results were analysed by the x^2 test for 2×2 contingency tables.

Results

As with our previous study, a high patient compliance rate was achieved. Eighty-one patients returned at 7 days and the remaining 9 were contacted, reporting no problems.

Pre-operative scrotal swabs cultured skin flora only with the exception of one patient who grew *Staphylococcus aureus*. He was in Group II and developed a wound infection.

Table 1 shows the clinical infection rate in the two groups. The reduction in rate from 37.8 to 6.7% is significant at the 1% level.

Table 2 shows the organisms cultured from the wound swabs. In nine of the 17 clinical wound infections in Group I and two of the 3 infections in Group II, pathogens were isolated. These were not present on the scrotum pre-operatively except for the one case in Group II reported above. This gives rates, where pathogenic organisms were found, of 20 and 4.4% respectively, the result also being significant.

Discussion

The control group showed a high infection rate (37.8%). This correlates well with the infection rate of 37.5% for the pre-operative chlorhexidine gluconate group in our previous study (Randall *et al.*, 1983) and is not significantly different from the overall infection rate in that study (32.9%). The reproducibility of these results confirms our initial finding of a high infection rate and justifies our use of the pre-operative chlorhexidine group as a control.

The diagnosis of wound infection is primarily a clinical one and the failure to culture conventional pathogens from a wound does not mean that it is not infected.

Table 1 Post-operative Wound Infection at 7 Days

	Chlorhexidine pre-op. *Group I*	*Chlorhexidi pre- and po op.* *Group II*
Infection absent	28	42
Infection present:		
Purulent	1	1
Serous	16 (17)	2 (3)
Total	45	45
Percentage infected	37.8*	6.7

* $P < 0.01$.

Table 2 Infecting Organisms

Organism	*Chlorhexidine pre-op.* *Group I*	*Chlorhexidi pre- and po. op.* *Group II*
Staphylococcus aureus	5	1
Coliforms	2	1
Pseudomonas spp.	1	—
Peptostreptococcus spp.	1	—
Skin flora:		
Staphylococcus epidermidis	8	1
Diphtheroids		
Total	17	3

Our infection rate is much higher than th reported by other workers but most studies do n define wound infection. Schmidt (1975) consider infection to be present in those patients requiri antibiotics and we must conclude that the presen of a purulent discharge is the criterion used l other workers. If we consider only our cases of pur lent discharge then our infection rate approach the figures reported in the literature. Howeve we have shown that patients with a serous di charge may grow pathogenic organisms, notab *Staphylococcus aureus*, and we consider the patients as having a wound infection. These infe tions were mild but could not be ignored because the small but real risk of complications and t possibility of loss of time from work.

We suggest that some workers may have artificially low infection rate if they define or purulent wounds as being infected. In additio some infections may be missed because of probler of follow-up. In this country most vasectomies a performed on a day-case basis and mild infecti may not come to the attention of the hospi doctor, being treated by the general practitioner

We feel that we have detected previously unrecognised infections and this finding may not be restricted to Salford.

The results of our initial study (Randall *et al.* 1983) agree with those of other workers (Ayliffe *et al.*, 1983; Leigh *et al.*, 1983), that the pre-operative use of chlorhexidine gluconate significantly reduces the skin flora but does not decrease the wound infection rate. This study shows that if, in addition, vasectomy patients also take post-operative chlorhexidine showers, then wound infection, on both clinical and microbiological grounds, can be significantly reduced.

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The Authors

P. E. Randall, FRCS, Lecturer in Surgery.

L. A. Ganguli, MB,BS, PhD, Dip Bact, Consultant Microbiologist.

M. G. L. Keaney, MB,BCh, BAO, MRCPath, Consultant Microbiologist.

R. W. Marcuson, MChir, FRCS, Consultant General Surgeon.

Requests for reprints to: P. E. Randall, Accident and Emergency Department, Hope Hospital, Eccles Old Road, Salford, Manchester M6 8HD.

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DNA Content of Human Semen—an Objective Measurement of Sperm Density

D. F. BADENOCH, C. G. FOWLER, P. R. EVANS and P. A. LOWREY

Department of Urology, The London Hospital and The London Hospital Medical College, London

Summary—In this study we have adapted a well tried and sensitive fluorometric assay for DNA that uses m-diamino benzoic acid (DABA) for its reaction with deoxyribose which is cleaved by perchloric acid from DNA. We have confirmed that this is easily measured in human semen. The method has been used on 200 samples of semen from patients attending the Infertility Clinic and men attending before and after vasectomy to give a wide range of sperm density. The objective DNA estimation has been compared with sperm density measurement made by an experienced laboratory observer using the Makler chamber and making his observations in ignorance of the DNA estimations. There was good correlation between DNA concentration and sperm density. The experimental accuracy of the two methods was found to be comparable. The advantage of the method is its objectivity. However, its disadvantages are its cost in terms of time and material and it cannot be used to confirm post-vasectomy azoospermia because the method also measures DNA in leucocytes.

Since Jequier (1983) demonstrated considerable observer error when the same specimen of semen was examined by 26 different observers, we have been stimulated to look for a more objective method for measuring sperm density. At present the most commonly used methods are by direct counting, using either the Neubauer haemocytometer or the Makler chamber, the latter being preferred because it does not require dilution. Electronic counter mechanisms such as the Coulter counter have been used but have been shown to be very inaccurate over ranges less than 10 million per ml. Since the mature spermatozoon is largely made up of head and a large proportion of this contains deoxyribose nucleic acid (DNA), we wondered whether its concentration in semen would reliably parallel sperm density and prove to be more objective than the current methods for measuring sperm density.

The method we chose to measure DNA content of semen is based on that described by Kissane and Robins (1958) and later modified by Vytasek (1982). This is a sensitive fluorometric assay for DNA using m-diamino benzoic acid (DABA) for the reaction with deoxyribose which is liberated by perchloric acid, fluorescence being proportional to the amount of DNA present. Its advantages are that it is simple to perform, reproducible and requires no complex acid or alcohol extraction steps. It is specific for DNA, and it has previously been shown to be suitable for measurement of DNA in complex mixtures with protein and RNA.

Patients and Methods

Two hundred samples of semen from patients attending the Infertility Clinic and men attending before and after vasectomy were analysed. The sample was examined for sperm density by an experienced observer (PRE) using the Makler chamber. DNA estimation was made as follows: 100 µl of mixed semen were micropipetted and centrifuged at 3000 rpm for 10 min. The supernatant was removed by pipette and the cellular pellet

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Read at the 40th Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

disrupted in 50 µl of phosphate buffered saline (PBS) by ultrasound probe. Suitable dilutions were then made with PBS and the sample (20 µl) freeze dried. Standard samples of DNA were made up by serially diluting with 5 mM sodium hydroxide, giving concentrations ranging from 0.01 to 0.64 µg/20 µl. To the freeze dried specimens and standards was added 1M perchloric acid and the specimens were then incubated at 65°C for 40 min.

The fluorescing reagent was prepared by mixing 3 ml of 10 mM sodium bicarbonate in molar sodium hydroxide to 1 ml of 20% weight to volume DABA: 40 µl of the fluorescing reagent were added to the samples and incubated for 1 h at 37°C. They were left to cool, diluted with 3 ml of 1M HCl and fluorescence was measured on a fluorescence spectrophotometer at an emission wavelength of 500 nm and excitation mirror 399 nm. This gives a standard DNA regression curve. The values for DNA of the samples would then be obtained from this curve, the final results being expressed as DNA concentration µl of semen.

In order to determine which was the more accurate of the measurements made, *i.e.* sperm density or [DNA] of semen, specimens from 10 patients were each split into 5 aliquots to give 50 samples. These were then randomly numbered 1 to 50 and estimates of sperm density and [DNA] were made as described above, independently and in ignorance of each other.

Results

One hundred and ninety-one of the 200 specimens could be analysed; 9 were impossible to micropipette due to high viscosity. When presented graphically, plotting sperm density against [DNA] (Fig. 1), there was positive correlation (r = 0.753).

When comparing the accuracy of measurement of sperm density to that of [DNA], the code was broken to reveal the source of each of the 50 samples. The sperm density was plotted against [DNA] and again there was a positive correlation (r = 0.868). To compare the relative accuracies of the two measurements we estimated the Standard Errors from the Mean (SEM) for both sperm density and [DNA] for each of the original 10 specimens of semen. This is represented graphically (Fig. 2) as SEM for sperm density and SEM of [DNA] against mean of sperm density for each group. There was a measurable quantity of DNA even in the two azoospermic samples. In the three with mean sperm density of less than 30 million per ml, SEM for sperm density was comparable with that of [DNA]. At high values of mean sperm density, SEM for [DNA] was lower than that of sperm density.

Discussion

We have demonstrated that by this simple fluorometric assay, DNA estimation of semen is easily

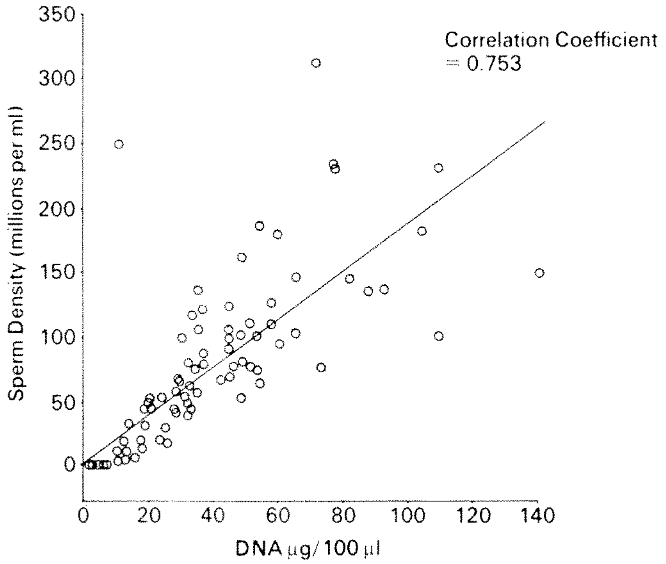

Fig. 1 Sperm density and DNA content of semen.

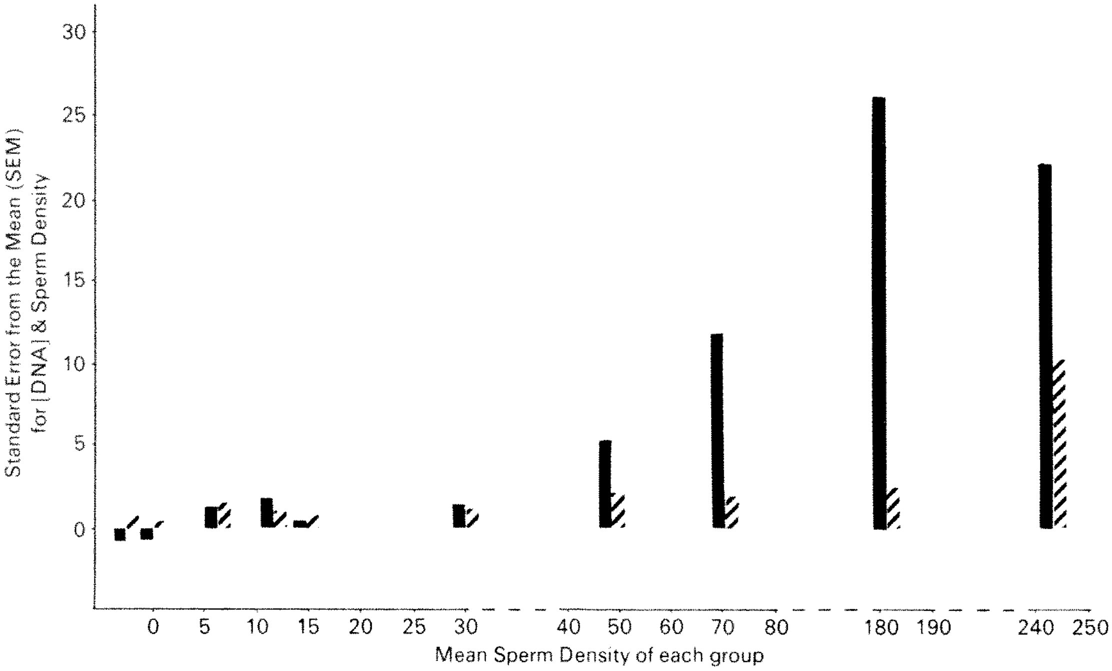

Fig. 2 Comparison of standard error from the mean vs mean sperm density. ■ = sperm density, ▨ = DNA.

made. There is good correlation between DNA concentration of semen and the sperm density except in azoospermia. Although this study shows that an experienced observer, using the Makler chamber, can be far more consistent than was found in Jequier's study, an objective method capable of giving equally accurate and repeatable measurements would have obvious advantages and at least in theory would be capable of being automated. All that would then be necessary would be to check for azoospermia as a simple test.

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The Authors

D. F. Badenoch, FRCS, Senior Registrar.
C. G. Fowler, FRCS, Lecturer.
P. R. Evans, Medical Laboratory Scientific Officer.
P. A. Lowrey, MSc, Medical Laboratory Scientific Officer.

Requests for reprints to: D. F. Badenoch, Department of Urology, The London Hospital, Whitechapel, London E1 1BB.

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Clinical Evaluation of the Heterologous Oocyte Penetration (HOP) Test

P. D. SUTHERLAND, P. L. MATSON, H. D. M. MOORE, R. GOSWAMY, J. H. PARSONS, P. VAID and J. P. PRYOR

St Peter's Hospitals and Institute of Urology; Department of Obstetrics and Gynaecology, King's College Hospital; Institute of Zoology, London

Summary—The heterologous oocyte penetration (HOP) test, using zona-free hamster oocytes, was used to assess the fertilising capacity of human spermatozoa. There was good correlation between the ability of ejaculated spermatozoa to penetrate the zona-free hamster oocytes and intact human oocytes. Using epididymal spermatozoa, the HOP test results showed that the ability to penetrate oocytes was acquired during their passage through the epididymis. Applied clinically, the HOP test enables a group of infertile men to be identified with a functional defect of their spermatozoa; these men may not be identified at routine seminal fluid analysis. Men with two negative HOP test results were confirmed as being infertile since their wives, if normal, conceived rapidly when donor spermatozoa were artificially inseminated.

The examination of seminal fluid (Pryor, 1981) does not provide an index of the fertilising capacity of spermatozoa, and so an additional test is now being developed which aims to determine the ability of the male gametes to penetrate ova. In particular, human spermatozoa have been shown to be capable of penetrating zona-free hamster oocytes (Yanagamachi *et al.*, 1976) under well defined conditions. In this study we have systematically compared the ability of spermatozoa to penetrate human oocytes and zona-free hamster oocytes, examined the development of the fertilising capacity of human epididymal spermatozoa and evaluated the clinical role of the heterologous oocyte penetration (HOP) test in the assessment of male partners of infertile marriages.

Patients and Methods

Male partners of infertile marriages produced semen specimens by masturbation, following 2 days' sexual abstinence, into wide-mouthed universal containers and the samples were processed within 1 h. Epididymal tissue was obtained from men undergoing vasectomy or epididymovasostomy under general anaesthesia who had given informed consent (Moore *et al.*, 1983). In 37 couples, human oocytes were aspirated using an ultrasonically-guided needle (Lenz and Lauritsen, 1982), and the corresponding HOP test was performed during the follicular phase of the woman's treatment cycle. In the HOP test (Tyler *et al.*, 1981; Matson *et al.*, 1984), suspensions of washed spermatozoa were adjusted to a constant density of 5 million/ml and pre-incubated for 18 h before insemination of the zona-free hamster oocytes. The definitive evidence of penetration was taken to be a spermatozoon, with a swollen head or male pronucleus attached to a tail, inside the egg vitellus. The results were considered as being either negative (no oocytes penetrated) or positive (one or more oocytes penetrated). All conceptions by the partners were noted and those couples where the man had two negative results were considered for artificial insemination by donor.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

Results

Fertilisation of human oocytes. There was good correlation between the penetration of human oocytes and zona-free hamster oocytes by human spermatozoa (Table 1), with concordant results being seen in 78% of cases.

Table 1 A Comparison of the Ability of Spermatozoa from 37 Men Participating in an *in vitro* Fertilisation Programme to Penetrate Human Oocytes and Zona-free Hamster Ova.

Human fertilisation	*HOP test result*	
	Negative	*Positive*
Negative	4	5
Positive	3	25

$\chi^2 = 5.07$, $P < 0.05$.

Epididymal spermatozoa. Epididymal spermatozoa first develop the potential to penetrate oocytes in the proximal corpus region (Table 2), whilst spermatozoa recovered from more proximal sites of the efferent duct failed to penetrate any oocytes.

Table 2 The Ability of Human Epididymal Spermatozoa to Penetrate Zona-free Hamster Oocytes

Region of epididymis	*Progressive spermatozoal motility (%)*	*No. oocytes penetrated*	*(%)*
Caput	3	0/51	(0)
Proximal corpus	12	3/28	(3)
Distal corpus	30	2/13	(11)
Cauda	60	33/76	(43)
Ejaculated spermatozoa	65	40/58	(68)

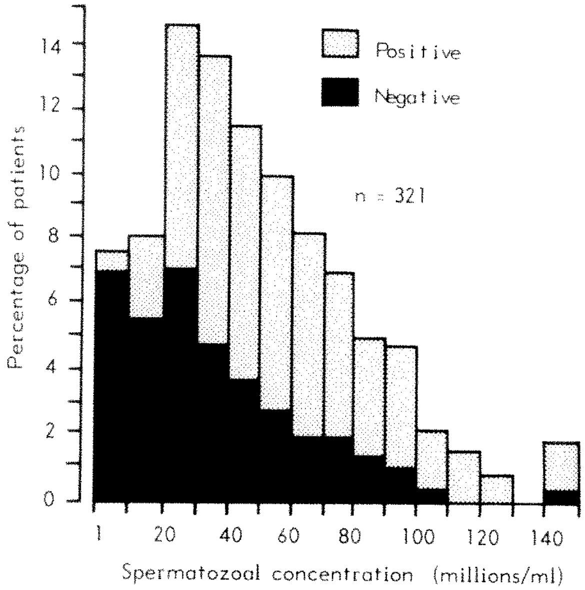

Fig. 1 The relationship between spermatozoal concentration in the test ejaculate and the result of the HOP test.

Table 3 Results of the HOP Test and Subsequent Conception in 168 Partners

HOP test result	*No. couples*	*(%)*	*Normal wife*	*No. conceived*	*(%)*
Positive	81	(50)	36	15	(42)
Variable	15	(9)	6	0	(0)
Negative	68	(41)	44	5	(11)

$\chi^2 = 4.31$, $P < 0.05$.

Table 4 Duration of Infertility Compared with a Subsequent Course of AID and its Outcome in 10 Wives of Men with 2 Negative HOP Tests

Patient	*Duration (months)*		*Outcome*
	Infertility	*AID treatment*	
1	84	3	Not pregnant
2	72	5	Not pregnant
3	121	6	Pregnant
4	84	2	Pregnant
5	60	6	Pregnant
6	98	6	Pregnant
7	36	8	Pregnant
8	36	6	Pregnant
9	36	6	Pregnant
10	36	3	Pregnant

Clinical application. The range of spermatozoal concentration (Fig. 1) and motility (Fig. 2) in the test ejaculates was similar for men giving either negative or positive HOP test results. The number of normal women spontaneously conceiving after their partner had scored a positive HOP test result (Table 3) was significantly greater than their counterparts with negative results. Ten couples with long-standing infertility, in which the wife was found to be normal and the husband had two negative HOP test results, opted for artificial donor insemination, and 8 of the wives conceived following 2 to 8 inseminations (Table 4). A single negative HOP test was sometimes followed by a test when

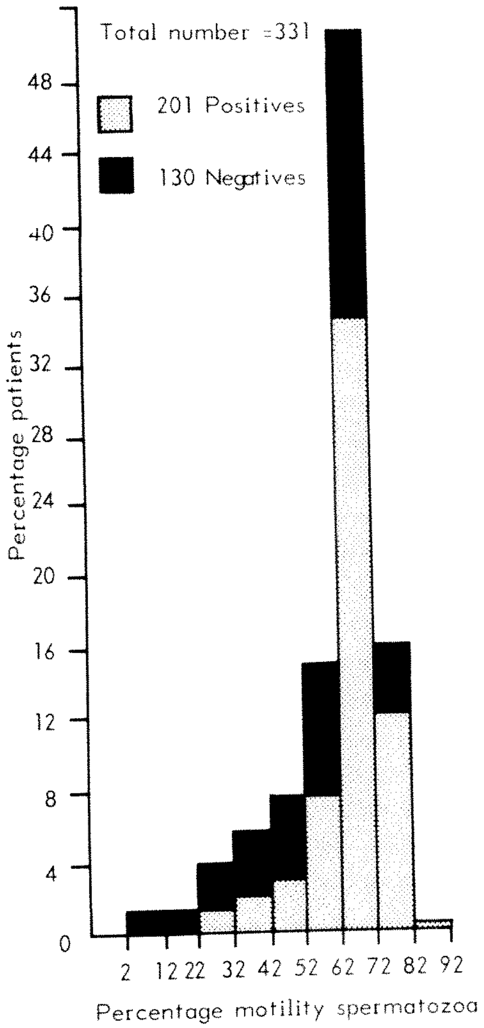

Fig. 2 The relationship between spermatozoal motility in the test ejaculate and the result of the HOP test.

only one oocyte was penetrated. The conversion of a negative HOP test was seen in one patient following treatment of a subclinical genital tract infection and in two patients whose semen contained gardnerella organisms. Two sets of brothers with long-standing infertility had negative HOP tests, although the wife of one subsequently conceived (paternity not established).

Discussion

Using spermatozoa from men participating in an *in vitro* fertilisation (IVF) programme, a significant correlation was obtained between the ability to fertilise oocytes from the wife and penetrate zona-free hamster oocytes. Similar results have been obtained by Margalioth *et al.* (1983a), validating the use of such surrogate oocytes in the determination of spermatozoal fertility, and showing the potential of the HOP test in screening patients for inclusion in an IVF programme. The surgical removal of epididymal tissue from men undergoing vasectomy or epididymovasostomy enabled the isolation of spermatozoa from defined regions of the epididymis. In this study, spermatozoa in the corpus region first showed the ability to penetrate the oocytes; whilst Hinrichsen and Blaquier (1980) showed an increase in the ability to bind to the oolemma as spermatozoa progressed through the epididymis, they found that the potential for penetration only became manifest in the cauda region.

The main clinical application of the HOP test is in the investigation of male fertility. In the present study, the result of the HOP test could not be predicted in the majority of cases from either the spermatozoal concentration or motility in the original ejaculate, and so the HOP test proved uniquely valuable in the identification of a group of infertile men with a functional defect of their spermatozoa. Hall (1981) also found the HOP test useful, and this is in marked contrast to Wickings *et al.* (1983) who could gain no further information about their patients over and above routine seminal analysis. The validity of the HOP test is difficult to gauge from spontaneous pregnancies because of the incidence of undetected female problems and infidelity. However, good indirect evidence can be obtained by artificial insemination with donor spermatozoa. As suggested by Margalioth *et al.* (1983b) from a small series of three patients, those wives of men giving negative HOP test results became pregnant in a relatively short period of time, showing that indeed there was a functional defect of the husbands' spermatozoa as detected by the HOP test.

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The Authors

P. D. Sutherland, FRACS, Clinical Research Fellow, St Peters Hospitals.

P. L. Matson, BSc, Scientific Research Assistant, King's College Hospital.

H. D. M. Moore, PhD, Research Scientist, Institute of Zoology.

R. Goswamy, MRCOG, Clinical Research Fellow/Honorary Senior Registrar, King's College Hospital.

J. H. Parsons, MRCOG, Lecturer/Senior Registrar, King's College Hospital.

P. Vaid, BSc, Scientific Research Assistant, King's College Hospital.

J. P. Pryor, MS, FRCS, Consultant Urologist, St Peters Hospitals.

Requests for reprints to: J. P. Pryor, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

British Journal of Urology (1985), **57**, 237-247

Case Reports

Malignant Fibrous Histiocytoma Involving the Bladder

A. G. TURNER, *Department of Urology, Charing Cross Hospital (Fulham), London*

Malignant fibrous histiocytoma is a rare tumour (Mackenzie, 1975). It originates in the cells with the potential of forming histiocytes or facultative fibroblasts.

Case Report

A 57-year-old lady presented with a 4-month history of pain on micturition and intermittent haematuria with clots. There were no other urinary symptoms. There was no previous history of serious illness.

On examination of the abdomen there was slight suprapubic tenderness. There were no other abnormal physical signs. Results of investigations were as follows: Hb 13.1 g/dl. ESR 53 mm/h. Serum electrolyte and urea—normal. MSU: RBC 50, WBC 50, no growth. IVU: large filling defect in the left side of the bladder. Cystoscopy: a large necrotic tumour occupying the left and posterior walls of the bladder. Bimanually there was an 8-cm mobile mass clinically stage T3. A biopsy was taken which showed the features of a malignant fibrous histiocytoma involving the bladder. Chest X-ray, pedal lymphography and isotope scan showed no evidence of metastatic disease.

Cobalt therapy was given to a dose of 6000 rads. Follow-up at 18 months showed no evidence of local or metastatic disease.

Comment

The histological diagnosis of malignant fibrous histiocytoma is based on the proportion of facultative fibroblasts (spindle cells) to histiocytes and the presence of intermediate forms, often multinucleated; granulomatous features may also be present. This biopsy showed a connective tissue tumour comprised of numerous large histiocytes, some with bizarre-shaped nuclei, numerous fibroblasts and areas of inflammatory granulation tissue, and confirmed a diagnosis of malignant fibrous histiocytoma involving the bladder (Fig.).

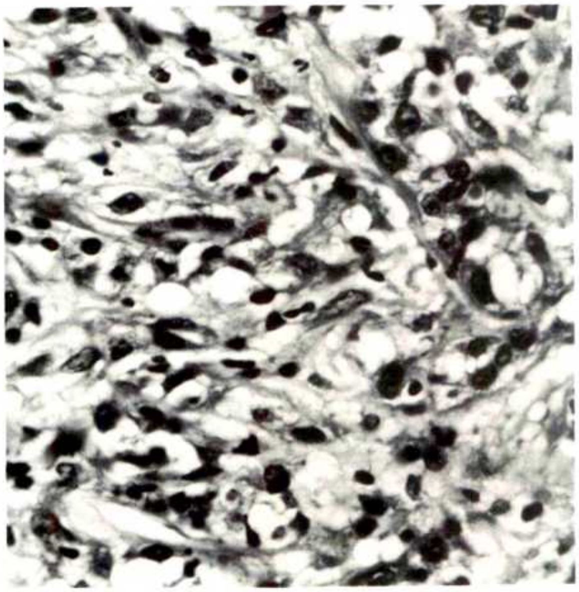

Fig. H and E × 356.

Malignant fibrous histiocytomas usually occur in middle age and have a sex incidence ratio male to female of 2:1. Usually the primary tumours are in skin, subcutaneous tissues or muscles. Tumours have also been reported in the retroperitoneal tissues or viscera, cervix uteri and kidney. Barsoum *et al.* (1979), however, found no record of the tumour involving the bladder. Metastases are found in lymph nodes, lungs and bones (Wasserman and Stuard, 1974).

In the case reported the tumour may be either a primary or a metastasis. There was no evidence of primary tumour in any other site and no evidence of other metastatic disease, since the lymphangiogram was normal. It seems, therefore, that the tumour is primary in the bladder.

Treatment in most cases has been by wide surgical excision since the tumours tend to be only moderately radiosensitive. An aggressive surgical approach to treatment is recommended (Barsoum *et al.*, 1979), as they tend to recur after radiotherapy. This case has responded dramatically to radiotherapy, there being no clinical evidence of tumour or histological evidence on random bladder biopsy.

Acknowledgement

I thank Mr Grant Williams, Consultant Urologist, for permission to publish this case and Dr B. Fox, Consultant Pathologist, for examination of the biopsy material.

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Requests for reprints to: A. G. Turner, Department of Urology, Peterborough District Hospital, Thorpe Road, Peterborough.

Primary Malignant Lymphoma of the Bladder

D. R. GUPTA, A. M. GILMOUR and J. P. WARD,
Departments of Urology and Pathology, District General Hospital, Eastbourne

Malignant lymphoma arising in the bladder is one of the rarest extranodal lymphomas. A new case is reported and the literature reviewed.

Case Report

An 80-year-old man presented with a 4-year history of intermittent haematuria, urinary frequency, poor stream and occasional hesitancy. Cytoscopy revealed a mass in the left lateral wall of the bladder which was irregular, nodular and was confluent with the left and middle lobes of the prostate. There were many vessels on the surface, although the mucosa appeared normal. Transurethral resection of this mass together with 44 g of the prostate was performed. It could not be established at operation whether this was a primary prostatic or bladder tumour. Histologically the bladder tumour showed sheets of lymphoid cells in the submucosa and muscle, the cells showing irregular contorted nuclei and frequent mitoses (Figs 1 and 2). The prostate showed fibroadenomatous hyperplasia and some fragments were infiltrated with tumour similar to that seen in the bladder. The appearances of this tumour were characteristic of a malignant lymphoma.

Post-operative recovery was uneventful but on the nineteenth post-operative day the patient suddenly collapsed and died. A post mortem examination revealed massive pulmonary embolism following deep vein thrombosis. The bladder showed ulceration and infiltration of the wall by the tumour. Significantly, no evidence of the lymphoma was found at any other site.

To date only 42 cases of lymphoma arising in the bladder have been reported. This tumour must be distinguished histologically from undifferentiated carcinoma in view of its better prognosis due to its radiosensitivity. Reactive lymphoid tissue present in chronic cystitis also must not be confused with lymphoma.

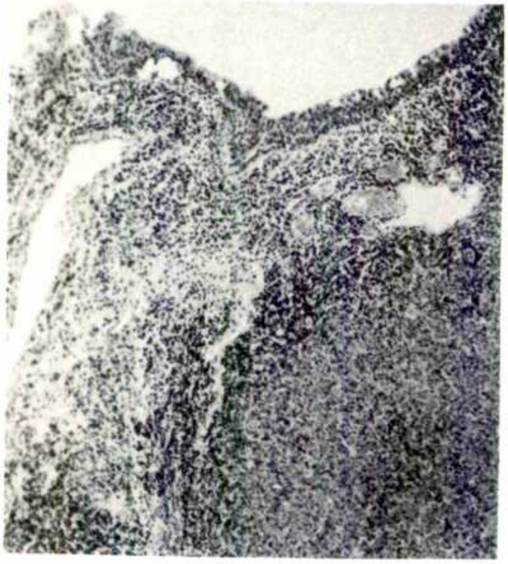

Fig. 1 Beneath the bladder epithelium (top left) lies a dense sheet of tumours cells. (H and E × 63).

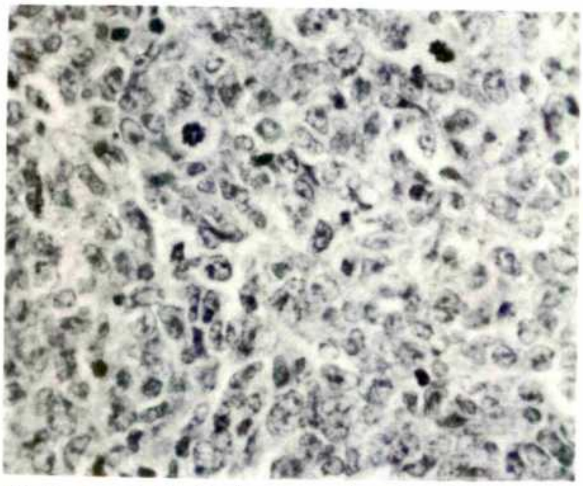

Fig. 2 Lymphoid cells showing much nuclear pleomorphism and several mitoses. (H and E × 400).

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Requests for reprints to: J. P. Ward, Department of Urology, District General Hospital, Eastbourne, East Sussex BN21 2UD.

Accidental Urethrocutaneous Fistula

A. L. WONG, C. G. MORRAN, A. McGEORGE and B. J. ABEL, *Department of Urology, Victoria Infirmary, Glasgow*

Case Report

A diabetic male, aged 69 years, was referred for investigation of urinary tract infection.

A wide urethrocutaneous fistula arising from the ventral aspect of the coronal sulcus was found on physical examination (Fig.). The prepuce was normally developed and the urethra permitted easy instrumentation. Micturition was accomplished largely via the external urethral meatus with only minor dribbling from the fistula.

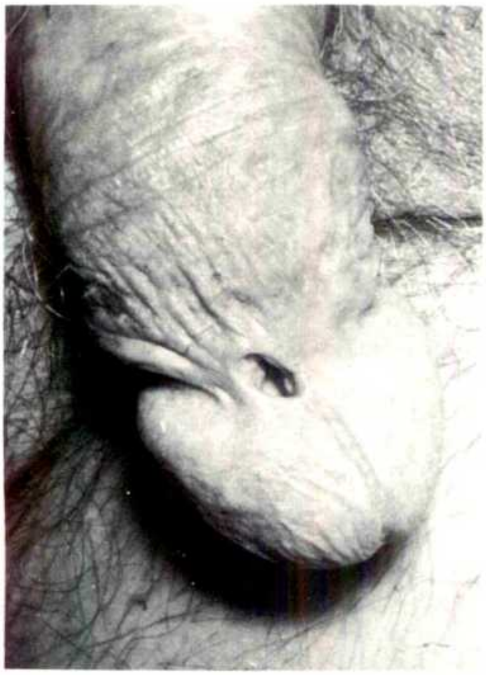

Fig. Urethrocutaneous fistula on ventral aspect of coronal sulcus.

It emerged on questioning that balanitis had been troublesome several years earlier. Having a self-reliant disposition, the patient had washed the area with a solution of Condy's crystals (potassium permanganate). To ensure thorough treatment he had placed a few crystals beneath the foreskin before retiring for the night. The result was an accidental urethrocutaneous fistula.

Comment

Potassium permanganate in solution has been used for many years for its disinfectant and astringent properties. Recommended dilutions vary from a 1:100 aqueous solution for the cleansing of ulcers, a 1:4000 solution as a vaginal douche and a 1:10,000 solution for urethral irrigation (Wade, 1977). In our unusual case the undiluted crystals caused tissue necrosis and fistula formation.

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Requests for reprints to: B. J. Abel, Department of Urology, Victoria Infirmary, Glasgow G42 9TY.

A Pararenal Pseudocyst of Unusual Aetiology

J. WORRELL, *Royal Infirmary, Bradford*

Pararenal pseudocysts are well recognised following blunt abdominal trauma, and may also occur after surgery to the upper renal tract (Hudson and Hundley, 1967) or above an impacted calculus (Leemans and Kotowicz, 1977). This report describes such a cyst arising after colonic surgery.

Case Report

The patient, a 60-year-old man with known diverticular disease, presented with symptoms suggestive of a colovesical fistula; this was confirmed by radiology and cystoscopy. He then underwent a sigmoid colectomy and partial cystectomy from which he made a good recovery.

Three weeks after discharge from hospital he was readmitted complaining of anorexia, weight loss and constipation. Examination revealed a smooth, well defined mass on the right side of the abdomen, shown on intravenous urography to be a right pararenal pseudocyst arising as a result of rupture of the right renal pelvis (Fig. 1), secondary to a stricture at the lower end of the right ureter (Fig. 2).

This ureter was explored, the stricture excised and a Politano-Leadbetter reimplantation performed. His symptoms rapidly resolved and 3 months later a further intravenous urogram showed only slight dilatation of the upper right renal tract with free drainage to the bladder.

Comment

Intra-operative ureteric damage is a well known hazard. It is, however, unusual for such damage, or subsequent scarring, to produce a pararenal pseudocyst due to rupture of the high pressure pelviureteric system.

One case has been reported (Schupbach and Bensman, 1974) of such a cyst treated by nephrectomy. This case illustrates the successful resolution of a similar cyst after excision of the stricture and ureteric reimplantation.

Acknowledgement

I thank Mr B. K. Gray for permission to report a patient under his care.

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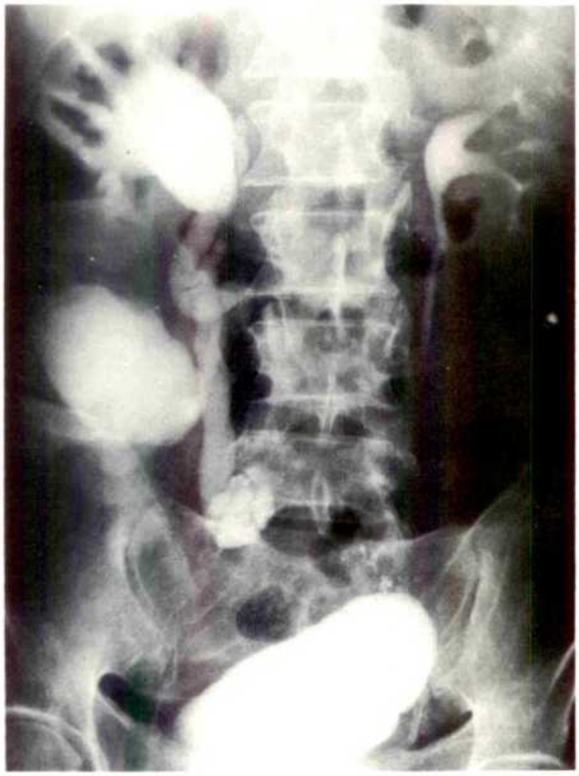

Fig. 1

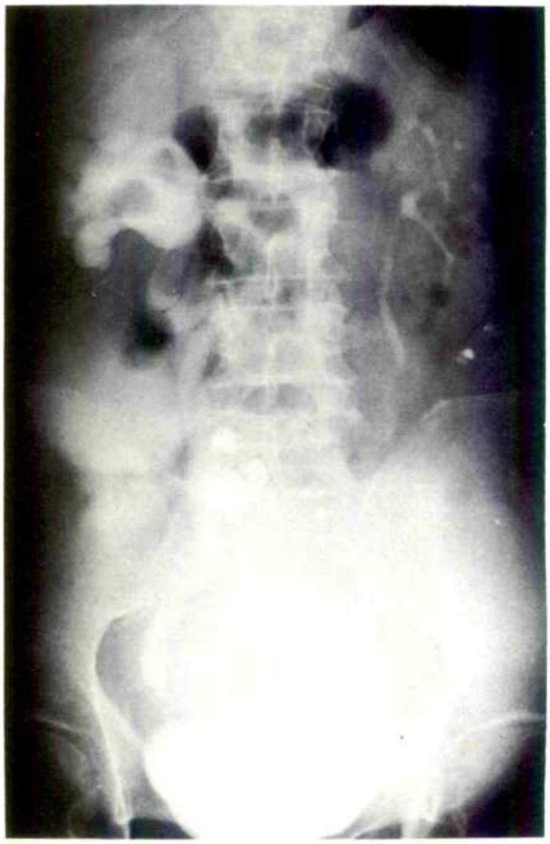

Fig. 2

Embryonal Rhabdomyosarcoma of the Prostatic-urethral Region in an Adult

D. J. M. KEENAN and W. H. GRAHAM, *Department of Surgery, Craigavon Area Hospital, Craigavon;* DOROTHY HAYES, *Department of Histopathology, Belfast City Hospital, Belfast*

Case Report

A 68-year-old man presented with intermittent urinary difficulty due to prostatic obstruction for 4 months. Clinical examination was negative. Urine analysis and intravenous urography were normal.

At operation the prostate was found to be partially replaced by a tumour which protruded into the urinary bladder at the urethral orifice as a yellow, glistening, grape-like mass. The tumour was resected along with the residual prostatic tissue.

The tumour weighed 100 g. Microscopy showed deep to intact urothelium, and infiltrating the prostate a tumour composed of small oval and stellate cells with a little pleomorphism in a loose myxomatous matrix (Fig. 1). A distinctive cambium layer was present (Fig. 2). Muscle striations were not identified but the features were sufficiently characteristic to allow diagnosis of an embryonal rhabdomyosarcoma.

Post-operative recovery was satisfactory. Radical surgery was not considered justified and the patient was given radiotherapy and chemotherapy. Eight months later the tumour recurred and the patient died 2 months afterwards from disseminated disease.

Comment

Embryonal rhabdomyosarcoma of the urogenital region predominates in early childhood (Bizer, 1969) and its occurrence in adult life is a rarity (Peterson and Paulson, 1974). This tumour arose in the prostatic-urethral area in a 68-year-old patient, and the gross and microscopic features were characteristic of an embryonal rhabdomyosarcoma. Identification of muscle cross-striations is desirable but their absence does not preclude the diagnosis in a tumour otherwise demonstrating distinctive pathology. An embryonal rhabdomyosarcoma has a poor prognosis despite surgery combined with radiotherapy and chemotherapy (Mackenzie *et al.*, 1971; Peterson and Paulson, 1974).

Acknowledgements

We are grateful to Miss R. Fox for typing the manuscript and to Mr J. Orchin for technical and photographic assistance.

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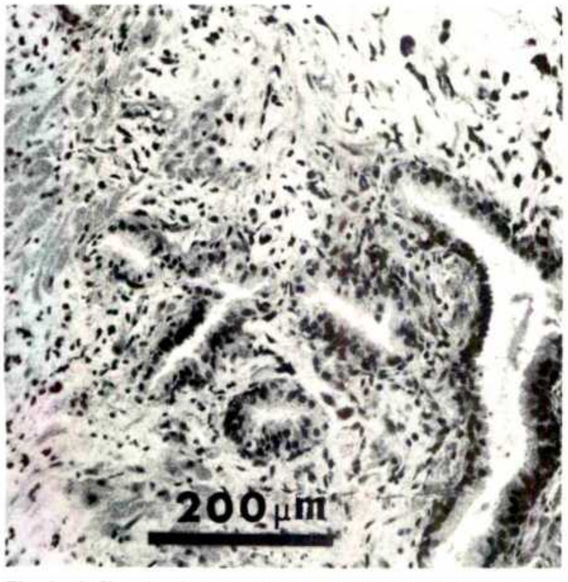

Fig. 1 Infiltration by tumour cells around prostatic glands. (H and E × 125).

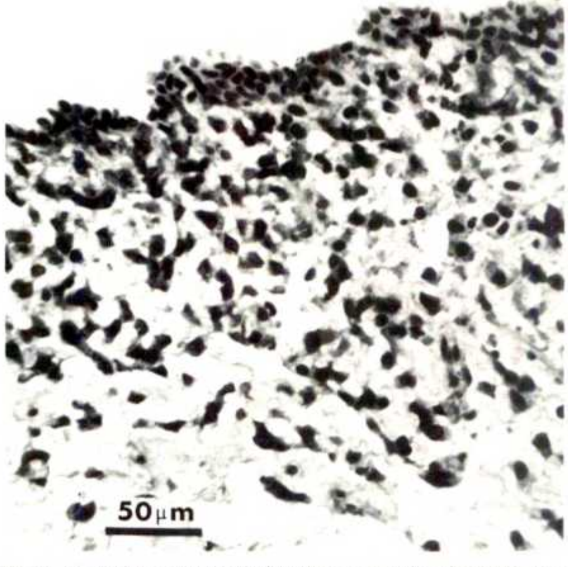

Fig. 2 Cambium cell layer with intact covering uroepithelium. (H and E × 252).

Urodynamic Changes Following Removal of a Large Ovarian Cyst

M. C. E. ORMISTON, J. L. OSBORNE and E. J. G. MILROY, *Department of Urology, Middlesex Hospital, London*

We describe the case of a young woman who presented with recurrent episodes of acute urinary retention due to a large ovarian cyst. She was found to have detrusor instability and vesical diverticula. Following removal of the cyst, the urodynamic behaviour and radiological appearance of her bladder returned to normal.

Case Report

L.B., aged 27 years, presented with frequency, a slow stream and difficulty in passing urine. On five occasions during the previous 10 months she had required catheterisation at another hospital for retention of urine.

On examination she was a fit woman with a tende suprapubic mass which was also palpable *per vaginam* There was no evidence of a neuropathy.

Before further investigations could be arranged she again developed acute retention of urine and was admitted as an emergency. She was catheterised and 1 litre of urine was drained from her bladder. After this procedure the mass felt in the out-patient clinic was still present.

A urodynamic videocystogram (Bates and Corney, 1971) showed that she had an unstable bladder with systolic contractions rising to 70 cm H_2O during filling to 400 ml capacity (Fig. 1), a raised voiding detrusor pressure of 60 cm H_2O and a slow flow rate of 12 ml/s, indicative of bladder outlet obstruction. During the examination she emptied her bladder completely. The bladder was seen to have trabeculae and several diverticula (Fig. 1), the changes being severe enough to suggest a suprasegmental neuropathy.

Cystoscopy showed a large extrinsic mass compressing the lower part of the bladder. At laparotomy this proved

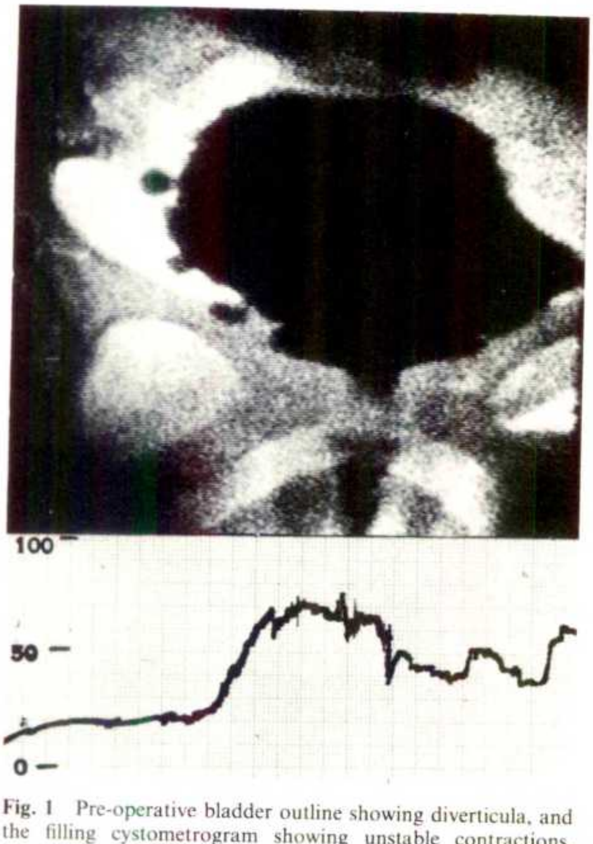

Fig. 1 Pre-operative bladder outline showing diverticula, and the filling cystometrogram showing unstable contractions, measured in cm H_2O.

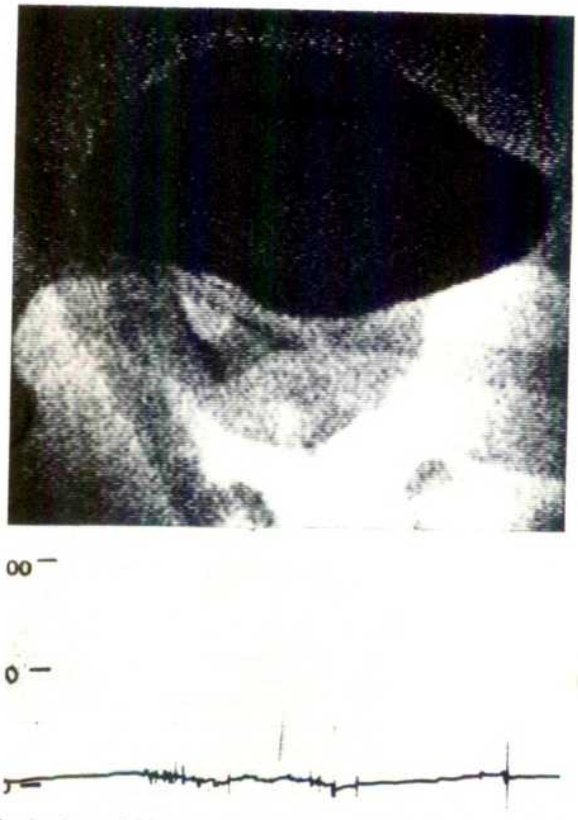

Fig. 2 Smooth bladder outline seen post-operatively, and the stable filling cystometrogram, measured in cm H_2O.

to be a grapefruit-sized benign ovarian cyst which was firmly lodged in the pouch of Douglas, displacing the bladder upwards. The cyst was removed.

Five months post-operatively her urinary symptoms had disappeared and no further episodes of retention had occurred. A repeat videocystogram demonstrated that her detrusor had reverted to normal stable behaviour on filling the bladder to 450 ml and her flow rate had improved to 15 ml/s, although the voiding pressure was unchanged. Remarkably, there was no sign of the trabeculae or diverticula seen pre-operatively (Fig. 2).

Comment

The use of videocystogram studies has made a great contribution to the understanding of voiding problems. Male and female bladders have very different urodynamic characteristics (Turner Warwick, 1979). Among men, detrusor instability is often consequent upon bladder outlet obstruction and in approximately 70% of cases stability returns after relief of the obstruction. In women the cause of detrusor instability is often difficult to define and is therefore difficult to treat. It is unusual for an unstable female bladder to revert to normal stable behaviour even after the relief of urodynamically confirmed bladder outlet obstruction (Farrar *et al.*, 1976).

In this case there was apparent extrinsic obstruction of the bladder outlet and the patient's bladder responded in a way characteristic of male bladders in the presence of obstruction. Furthermore, her bladder became dynamically stable after relief of the obstruction. We have seen only one comparable case in more than 6000 similar investigations performed in this unit. Equally strange is the radiological disappearance of the trabeculae and diverticula seen pre-operatively, and we believe that the latter were in fact "pseudo-diverticula".

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Requests for reprints to: M. C. E. Ormiston, 9 Stratford Villas, Camden Town, London NW1 9SJ.

Unilateral Renal Cortical Necrosis

M. L. BLUTE and A. C. TEMPLETON, *Department of Pathology, St Vincent Hospital, Worcester, USA*

Renal cortical necrosis is a result of failure of perfusion. Most of the 400 cases reported to date are bilateral and occur in pregnancy. Only nine cases of unilateral necrosis are reported, of which seven showed obstruction of the ureter on the protected side and the remainder showed renal artery stenosis on the protected side. In this patient neither of these two features was present, but the protected kidney contained a tubular carcinoma.

Case Report

The patient was an 86-year-old woman with congestive cardiac failure and chronic cystitis. She developed uraemia and died 4 days after a flare-up of cystitis. *Post mortem* showed a right kidney bearing a tumour extending into a vein (Fig. 1), and the left showed cortical

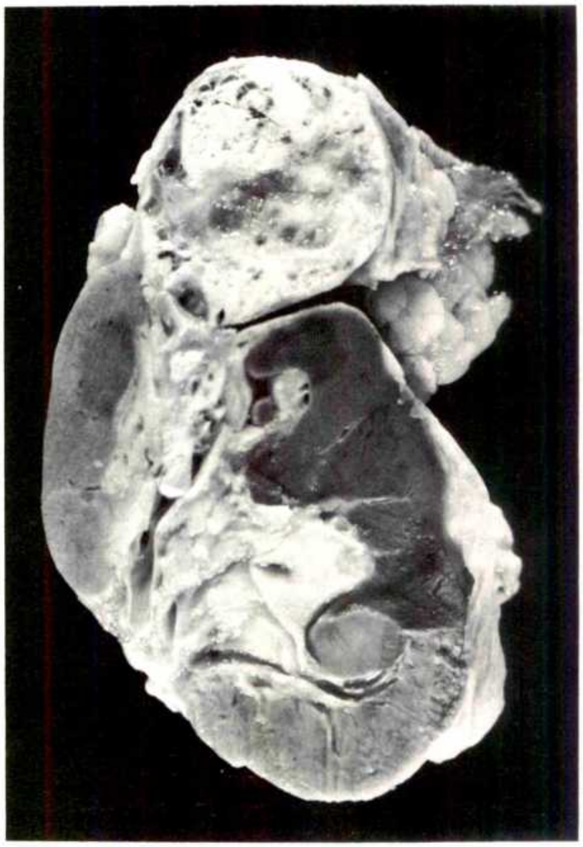
Fig. 1

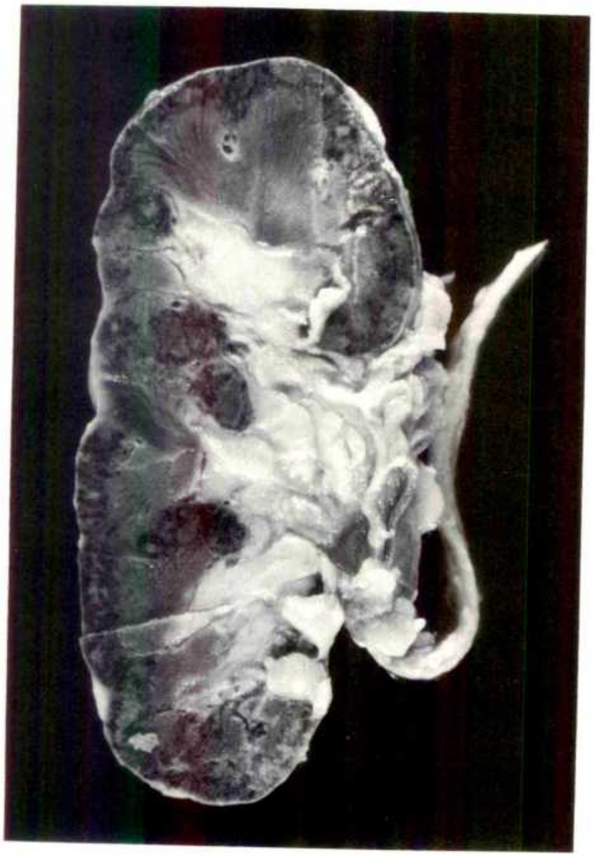

Fig. 2

necrosis (Fig. 2). The bladder contained infected urine. Other systems were unremarkable except for severe atheroma of vessels.

Comment

Cortical necrosis results from renal arterial spasm and develops only in a kidney producing urine. Ureteric obstruction therefore protects against its development (Watchi and Altman, 1970). Sometimes the spasm is induced by circulating toxins. Renal artery stenosis can protect the kidney by reducing the dose delivered to the vessel wall. Endotoxin has been shown to produce unilateral cortical necrosis in experimental animals (Raij *et al.*, 1977). The cortex of a kidney bearing a renal tumour is hypoperfused (Ofstad and Kolsaker, 1970). Chronically hypoxic kidneys develop arteriovenous shunts which are not sensitive to vasopressor effects.

We believe that our patient developed bacterial endotoxaemia following cystitis. The cortex of the tumour-bearing kidney received a lower dose of this material than the normal kidney, which was insufficient to induce necrosis.

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Requests for reprints to: A. C. Templeton, Department of Pathology, Rush Medical College, Chicago, Illinois 60612, USA.

Acute Suppurative Epididymitis in an Intra-abdominal Testis

K. E. HASSAN and P. CHUI, *Department of Urology, Monklands District General Hospital, Airdrie*

Case Report

A 16-year-old boy was admitted with a 2-day history of dysuria, frequency of micturition, nausea, vomiting and colicky central abdominal pain which later localised to the right iliac fossa.

His previous history was important. His mother had taken Thalidomide for 1 week during the first 3 months of pregnancy. At birth his anus was absent and a single large perineal opening drained the urinary system. Most of the right buttock was involved in a diffuse haemangioma. His penis was minute, his scrotum was bifid with an undescended right testis, and he had a high imperforate anus, bilateral hydronephrosis, bilateral vesicoureteric reflux and an abnormally shaped bladder with a distal urethral opening in the defect in the perineum. For these he had had a transverse colostomy followed by pull-through and later closure of the colostomy, excision of the perineal defect and urethral repair, and bilateral ureteric reimplantation.

Physical examination showed a thinly built boy. He was pyrexial (37.9 C). His abdomen was soft but there was marked tenderness in the right iliac fossa with no rebound tenderness. On rectal examination there was no tenderness or palpable mass. His left scrotum contained a small testis. Laboratory investigation showed haemoglobin 15.6 g/dl, white cell count 14.5 and normal urea and electrolytes.

An emergency laparotomy was performed through a grid-iron incision for suspected acute appendicitis. The appendix was normal but there was an intra-abdominal testis with an acutely inflamed epididymis. Orchiectomy was performed because orchiopexy was impossible, and this was followed by appendicectomy. The testis and epididymis weighed 18 g. Acute suppurative epididymitis was seen on microscopic examination. A midstream specimen of urine showed a significant growth of *Escherichia coli* (> 100,000/ml).

Comment

The intra-abdominal position is an unusual site for an undescended testis (Shapiro, 1978) and acute suppurative epididymitis in such a place is rare.

The aetiology of the undescended testis is poorly understood, though many theories have been postulated, such as hormonal and mechanical factors, hereditary autosomal anomalies and damage by environmental factors such as Thalidomide. True cryptochidism is usually associated with congenital inguinal hernia. Urinary tract anomalies such as double ureter, renal hypoplasia or ectopia and hydronephrosis occur in approximately 12% of asymptomatic cryptorchid boys over the age of 2 years (Warkany, 1971).

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Requests for reprints to: K. E. Hassan, Surgical Registrar, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

Point of Technique

Bladder Reconstruction after Cystectomy for Cancer: Use of the Ileal Reservoir

E. ALCINI, M. PESCATORI, A. D'ADDESSI, A. DESTITO and G. C. CASTIGLIONI, *Urological Division, Department of Surgery, Catholic University of the Sacred Heart, Rome, Italy*

The technique of the three-loop ileal reservoir has been modified and used in the surgical treatment of bladder cancer to restore urinary continuity after cystectomy. This procedure avoids some of the disadvantages associated with other procedures which use intestinal segments.

Several surgical procedures have been used to restore urinary continuity after radical cystectomy for bladder cancer and they all use an intestinal segment as a storage organ, which obviates the need for a permanent stoma and permits physiological micturition (Couvelaire, 1950; Gil-Vernet, 1965; Kuss *et al.*, 1970). However, they all have disadvantages. The small capacity of the ileum often leads to urinary frequency and the sigmoid is likely to be affected by pre-operative irradiation (Kuss *et al.*, 1970; Camey and Le Duc, 1979). The use of an ileocaecal segment requires particular anatomical conditions and often presents technical difficulties which increase operative time and carry a greater risk of post-operative complications (Alcini *et al.*, 1985).

The use of the ileal reservoir is an alternative procedure which can be adopted when ileocaecourethroplasty is difficult to perform because of technical problems. It has been shown that the ileal reservoir allows faecal continence after restorative proctocolectomy (Pescatori and Parks, 1984).

Technique

The abdomen is opened by a median supraumbilical incision. The bladder is excised together with the seminal vesicles and the prostate up to the verumontanum. Construction of the ileal reservoir, as described by Parks and Nicholls (1978) after restorative proctocolectomy, must be slightly modified: the three ileal segments are shorter (8 cm) and most of the terminal ileum is left intact. The capacity required to replace the urinary bladder is less than that needed for the rectum. Excision of the terminal ileum should be minimised in order to avoid metabolic disorders such as B_{12} and fat malabsorption. A 25-cm loop of small bowel is isolated at least 50 cm from the ileocaecal valve, with careful preservation of its vascular supply. An end-to-end anastomosis is then performed to restore intestinal continuity. The resected ileal loop is triplicated and a reservoir constructed (Fig. 1). A short efferent loop (2 cm) should be left to allow suturing to the prostatic cuff. The ureters are sutured to the proximal end of the afferent loop, 2.5 to 3 cm in length (Fig. 2). The ileal reservoir is placed outside the peritoneal cavity; 2/0 Vicryl

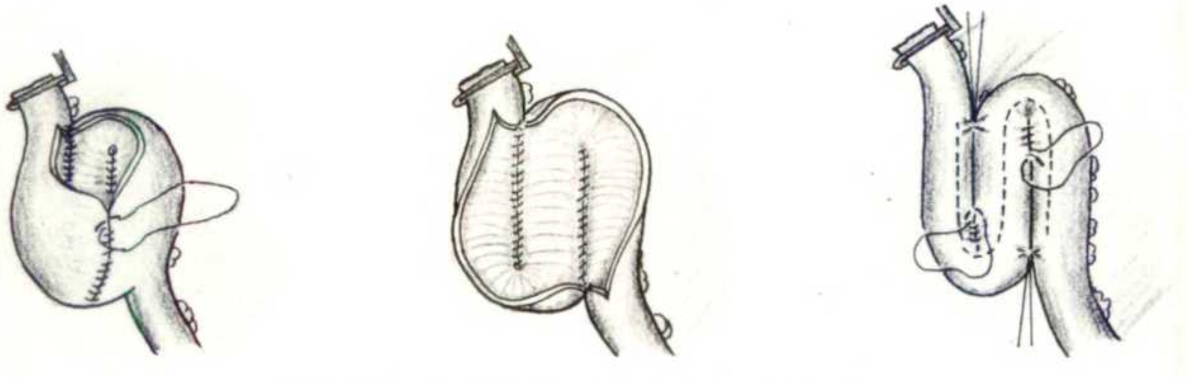

Fig. 1 Three consecutive stages of construction of the ileal reservoir.

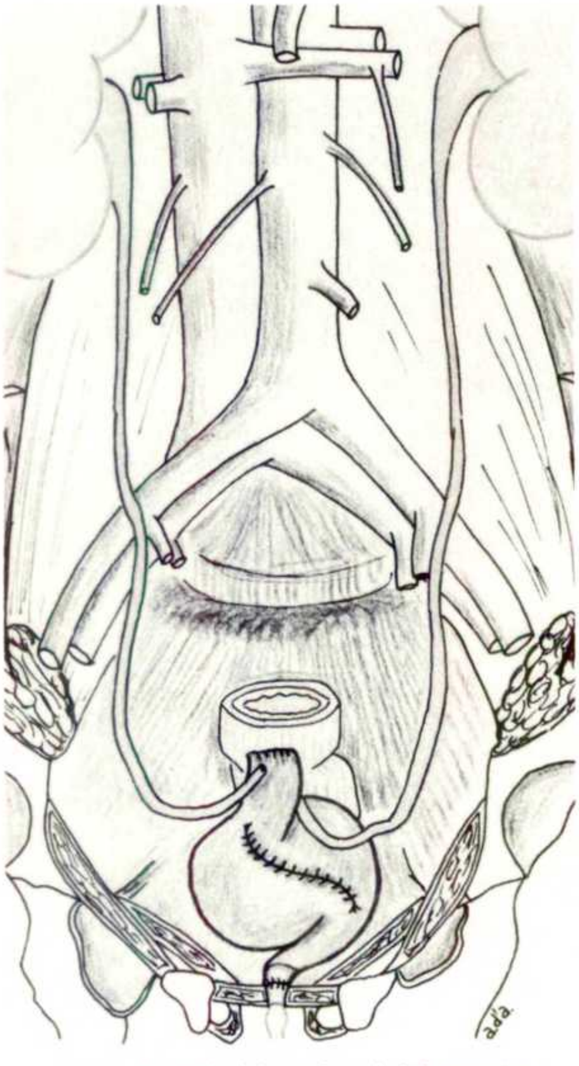

Fig. 2 Anatomical view at the end of the operation.

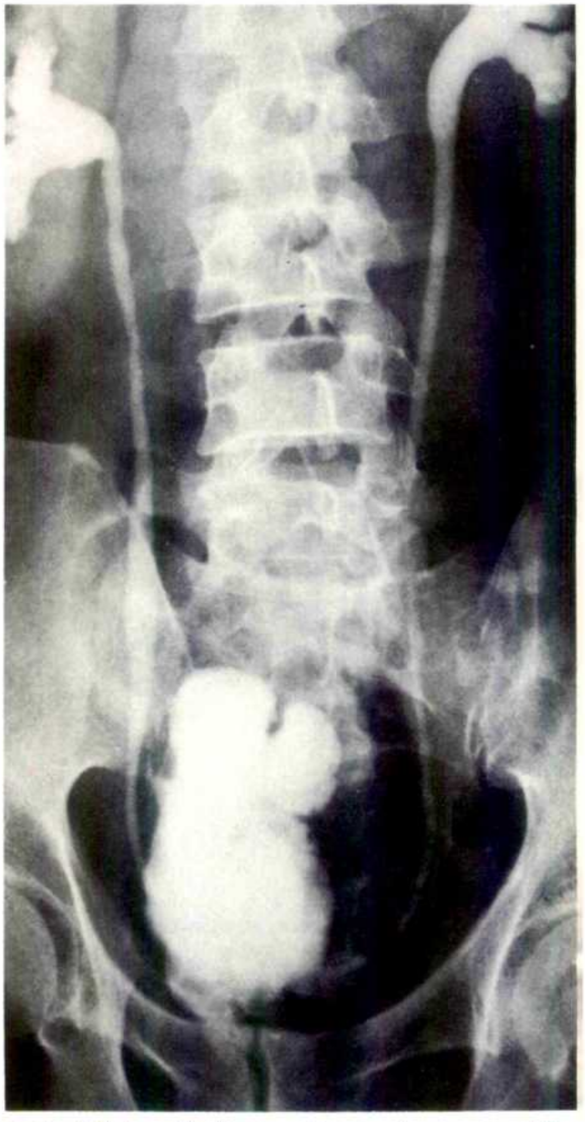

Fig. 3 IVU 1 month after operation showing capacity of the newly formed bladder.

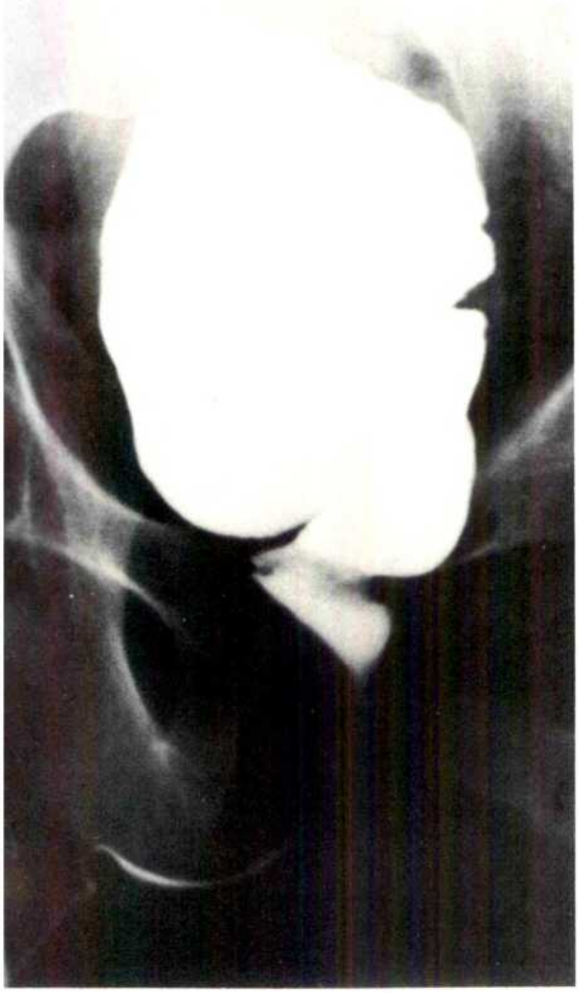

Fig. 4 Voiding cystography 8 months after operation.

sutures are used. A multifenestrated urethral catheter is inserted into the ileal pouch at the end of the operation, before closure of the abdominal wall. Post-operative radiographs show good results (Figs. 3 and 4).

The use of the ileum to restore urinary continuity after cystectomy is not new (Kuss *et al.*, 1970; Deklerk *et al.*, 1979). We believe that the three-loop ileal reservoir forms a satisfactory urinary storage organ in terms of morphology and capacity and it can be used when an ileocaeco-urethroplasty is technically impossible to perform.

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British Journal of Urology (1985), **57**, 248-249

Notices

British Association of Urological Surgeons

President: Professor J. P. Blandy, DM, MCh, FRCS, FACS

Annual Meeting: Eastbourne, 9-12 July 1985

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Edinburgh Urological Festival

Edinburgh. 28-30 August 1985

The Urological Festival is a post-graduate course of lectures by invited speakers and short papers by participants.

The main topics for the 1985 meeting include reconstructive urological surgery, psychosexual medicine, computers in urology, endo-urology and recent advances in chemotherapy.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Shackman Travelling Fellowship

The Fellowship for 1985 has been awarded to Mr A. C. Buck, Cardiff, to enable him to work in Munich University on the subject of "The influence of prostaglandins and their inhibitors on calcium transport in the kidney."

Multidisciplinary Course on Principles of Cancer Treatment

London. 30 April-3 May 1985

The course will be held at the Royal College of Surgeons and is non-residential. Course fee: £150.00.

Further particulars from: Courses Department, British Postgraduate Medical Federation, 33 Millman Street, London WC1N 3EJ. Telephone: 01-831 6222, Ext. 39.

Symposium on Investigating the Urinary Tract in Children

Selwyn College, Cambridge. 19-21 June 1985

The Cambridge summer meeting in residence is a regular event for interested radiologists and clinicians. About half of the programme is reserved for discussion between speakers and audience. Inclusive cost £105.

Further details from: Professor T. Sherwood, Department of Radiology, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

European Nuclear Medicine Congress 1985

London. 3-6 September 1985

Further particulars from: Congress Secretariat, Institute of Nuclear Medicine, Middlesex Hospital, Medical School, Mortimer Street, London W1N 8AA.

Belgian Society of Urology: 50th Congress

Brussels, Belgium. 8 and 9 June 1985

The topic will be "Testicular Tumours: a Multidisciplinary Approach". Further particulars from: Dr F. Wart, Institut Médico-chirurgical A. Gailly, Service d'Urologie, Boulevard Zoé Drion 1, B-6000 Charleroi, Belgium.

20th Congress of the International Society of Urology

Vienna, Austria. 23-28 June 1985

Topics

1. Ultrasound in diagnosis and treatment.
2. Emergency treatment of traumatic lesions in the urinary tract.
3. Bladder tumours: prognosis and treatment.

Round Tables

1. Laser in urology.
2. Treatment of testicular tumours.

Note: Only members of the International Society of Urology may participate in the Congress, but members may sponsor one colleague who wishes to attend.

Further particulars from: Secretariat, XXth Congress of the International Society of Urology, c/o Vienna Academy of Medicine, Alser Strasse 4, A-1090 Vienna, Austria.

12th Meeting of the International Study Group for Steroid Hormones

Rome, Italy. December 1985

The main topics of the meeting will be:

1. Steroid peptide interaction
2. Sex hormone antagonists.
3. Intratissular steroids and hormone dependent corneu.

Deadline for presentation of abstracts: 30th June 1985.

Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma, viale del Policlinico, 00161 Rome, Italy.

Seventh Congress of European Association of Urology

Budapest, Hungary. 26-28 June 1986

Further particulars from: Professor F. Balogh, Department of Urology, Semmelweis University of Medicine, Maria U. 39, 1085 Budapest VIII, Hungary.

Third International Forum of Andrology

Paris, France. 17-18 June 1985

The topics will be:
Androgens: mechanisms of action; therapeutic indications.
Epididymis: physiology, pathology.

The official languages will be French and English (simultaneous translations).

Further information from: Professor G. Arvis, Department of Andrology-Urology, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, F-75012 Paris, France.

British Journal of Urology (1985), **57**, 250

Book Reviews

Practical Urologic Endoscopy. By M. Miki. Pp. viii + 87. Tokyo/New York: Igaku-Shoin. 1983. Price $44.00.

It is difficult to know the exact aim of this book. Despite the title, the book cannot be recommended as a manual of operative technique for the urologist in training because there are significant omissions. For example, the endoscopic management of bladder tumours is inadequately covered and there is only brief mention of percutaneous nephroscopy. The main strength of the book is the excellent, although sometimes bizarre, colour photographs (*e.g.* cucumber in the bladder). There is also a good section on photography and useful descriptions of flexible cystoscopes and urethroscopes.

This book could be considered for the departmental library where there is specific interest in new developments in endoscopy. It cannot be recommended for all urological departments and the urologist in training must look elsewhere for a comprehensive manual of endoscopic technique.

Atlas of Urologic Endoscopic Surgery. By H. J. Reuter. Pp. ix + 252. Philadelphia, London, Toronto: Saunders. 1982. Price £64.50.

This book is partly an atlas and partly a manual of transurethral surgery. The author favours "low pressure transurethral resections" achieved by aspirating continuously the irrigating fluid through a suprapubic trocar inserted at the start of the procedure for extensive and difficult TURs, by using a continuous flow resectoscope for others. This technique, the author explains, reduces bleeding, prevents the TUR syndrome, increases operating time and causes fewer complications and deaths than other procedures.

The book also describes the author's method of endoscopic transurethral cryosurgery by which the developing iceball at the bladder neck is seen continuously through a cystoscope that is introduced into the bladder suprapubically. The author recommends this technique for poor risk patients with prostatic adenoma and for selected patients with T2 to T4 prostatic carcinoma, and in his hands it is attended by few complications.

The book is profusely illustrated with line diagrams and colour photographs that illustrate the procedures and their complications. It concludes with a statistical study of the author's experience of 3000 TURPs, not all low pressure ones, and 1203 cases of cryosurgery.

Hypercalciuric States: Pathogenesis, Consequenc and Treatment. Edited by F. L. Coe. Pp. xii + 44 New York: Grune and Stratton. 1984. Price $69.5

This book is a collection of 12 reviews, mostly mul authored, almost all of the authors being practising ph sicians from the Mid-Western states of the USA, wi some from California. The Editor is a justly respect figure in the field with a wide and deep knowledge of t clinical and laboratory applications and theoretical a pects of hypercalciuria.

The individual chapters are, in the main, exceller They are clearly written, as free of jargon as can expected in this day (especially in an area of such rap informational increment) and the references at the end each chapter are reasonably comprehensive. Most of t chapters are up-to-date and most review the significa literature up to 1981. The figures and tables are, with tv or three exceptions, clear and easy to understand. T index is adequate. A major quibble, however, is the la of uniformity in the use of the S.I. nomenclature fro chapter to chapter and even, on one or two occasior between figure or table and script in the same chapt This is a pity.

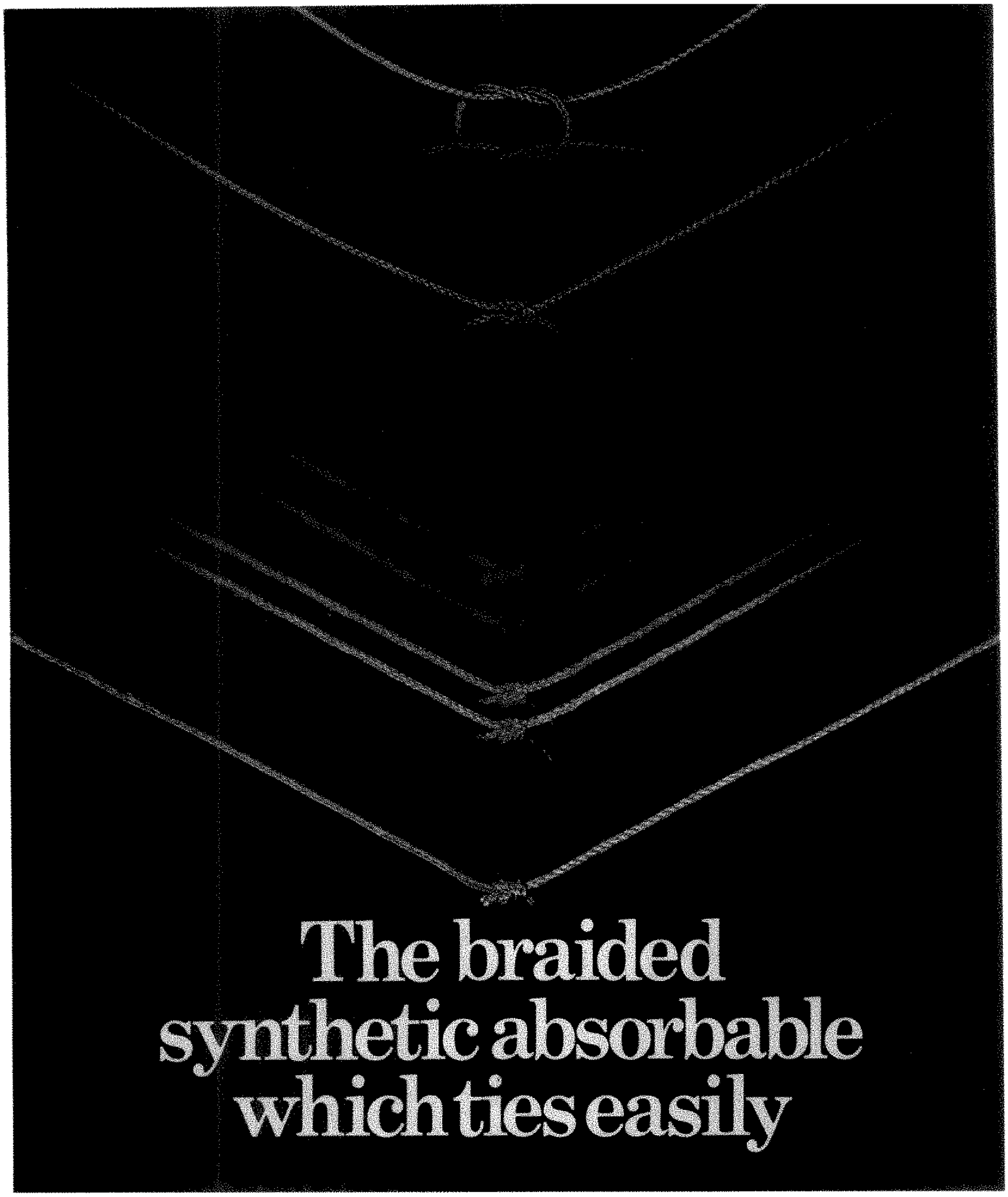
Most of the significant aspects of the subject of hype calciuria are dealt with; there is some repetition of su ject matter but this is often necessary for clarity exposition and argument.

This book will be useful for all clinicians and pos graduate students interested in hypercalciuria. Howeve despite its reasonable size, this is a volume more appr priate for the library reference shelf than for person ownership.

Books Received

Ontogeny of Bonding-Attachment. Progress in R productive Biology and Medicine. Volume 1 Edited by P. O. Hubinont. Pp. 178. Basel: Karge 1984. Price SFr. 145.-; DM 174,-; US$ 87.00.

Issues in Glomerulonephritis and Renin Systen Contributions to Nephrology, vol 43. Edited b E. Ritz and S. G. Massry. Pp. 203. Basel: Karge 1984. Price SFr. 132.-; DM 158.-; US$79.25.



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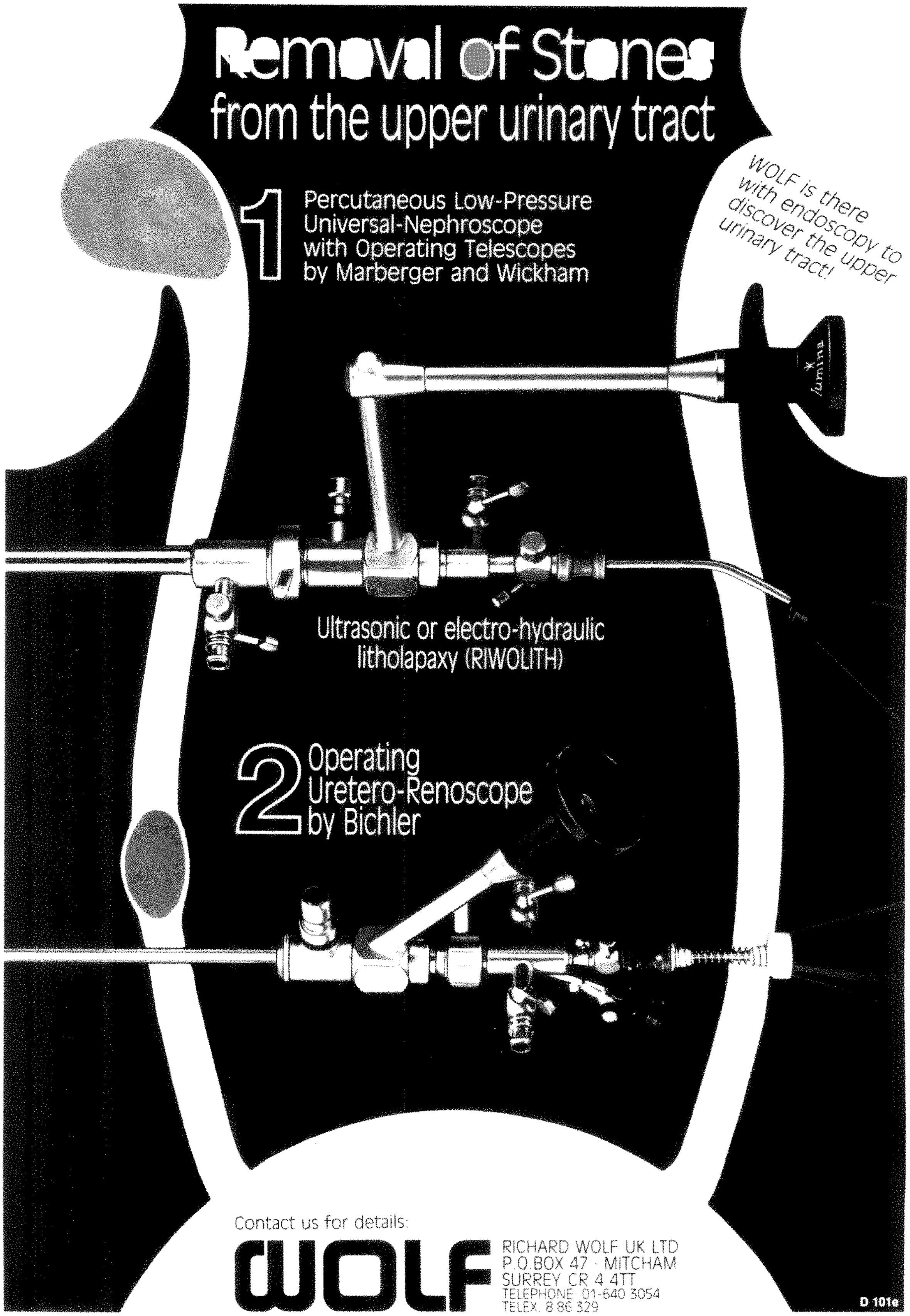

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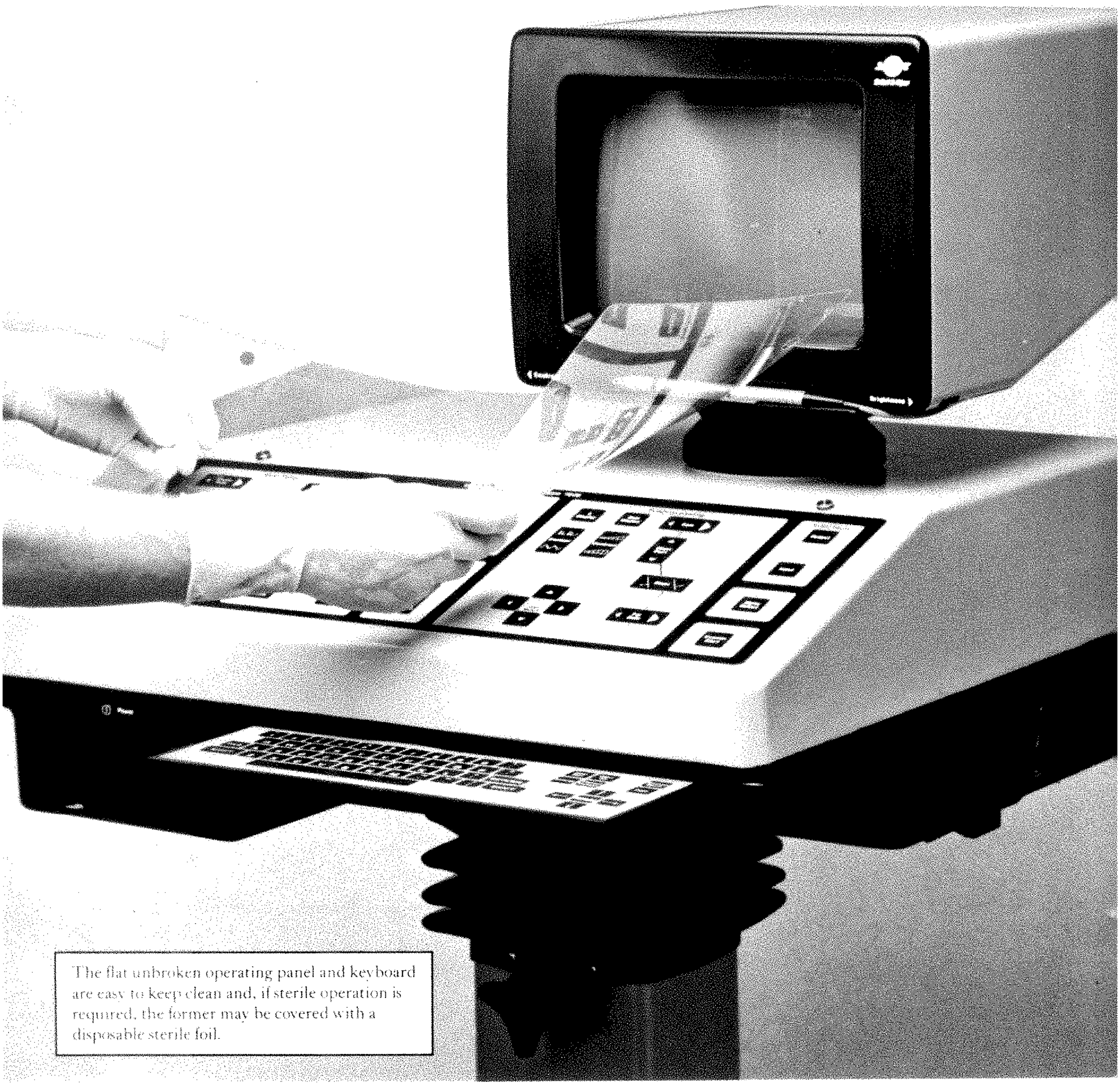

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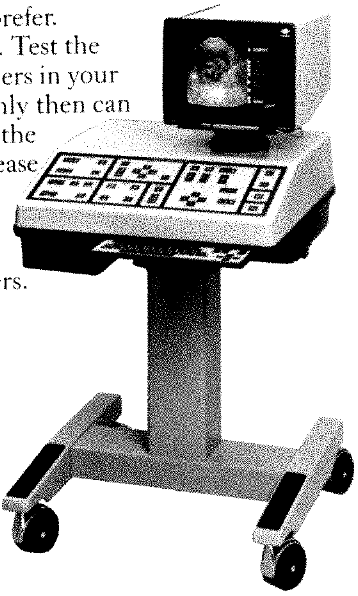

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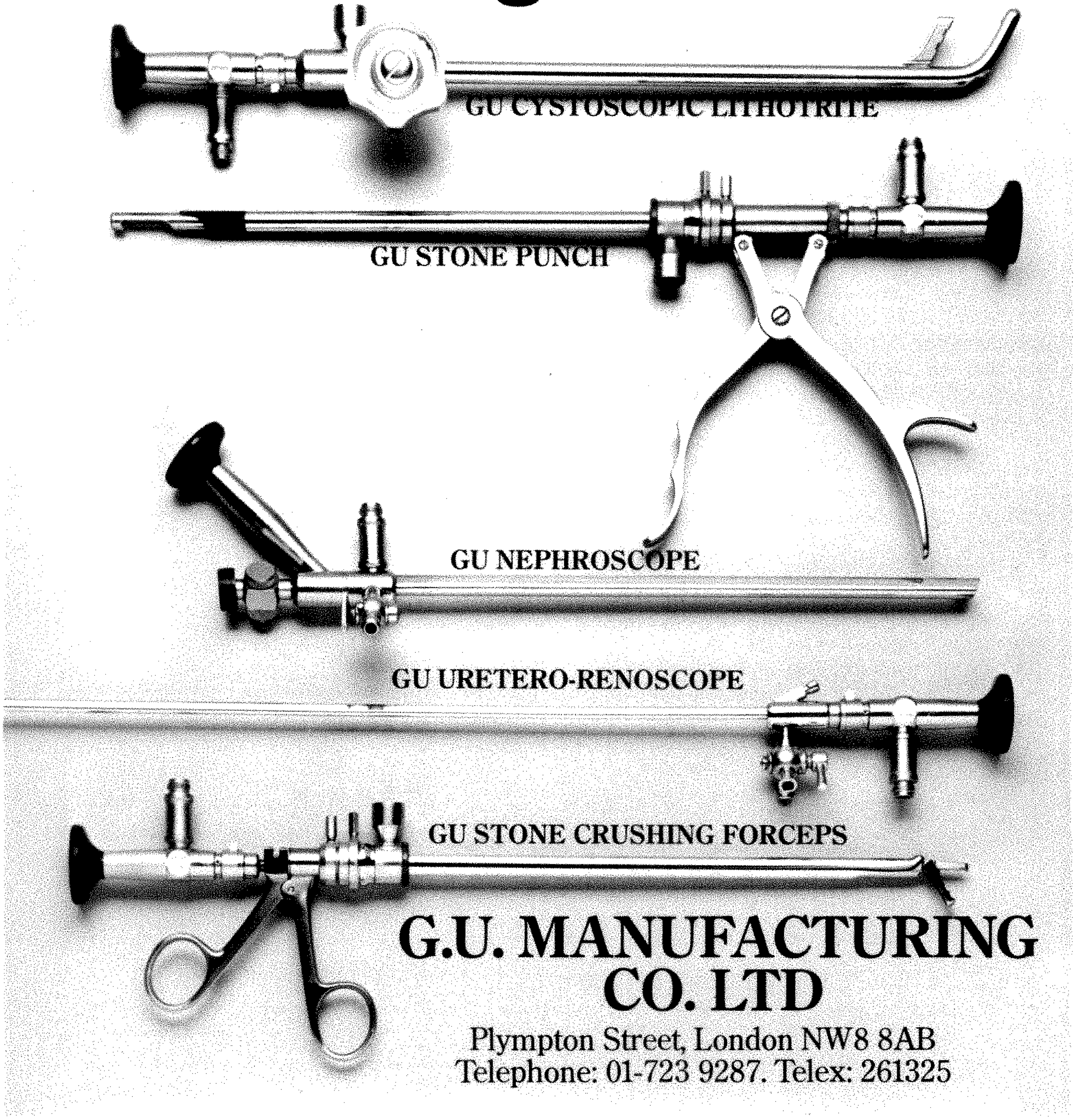

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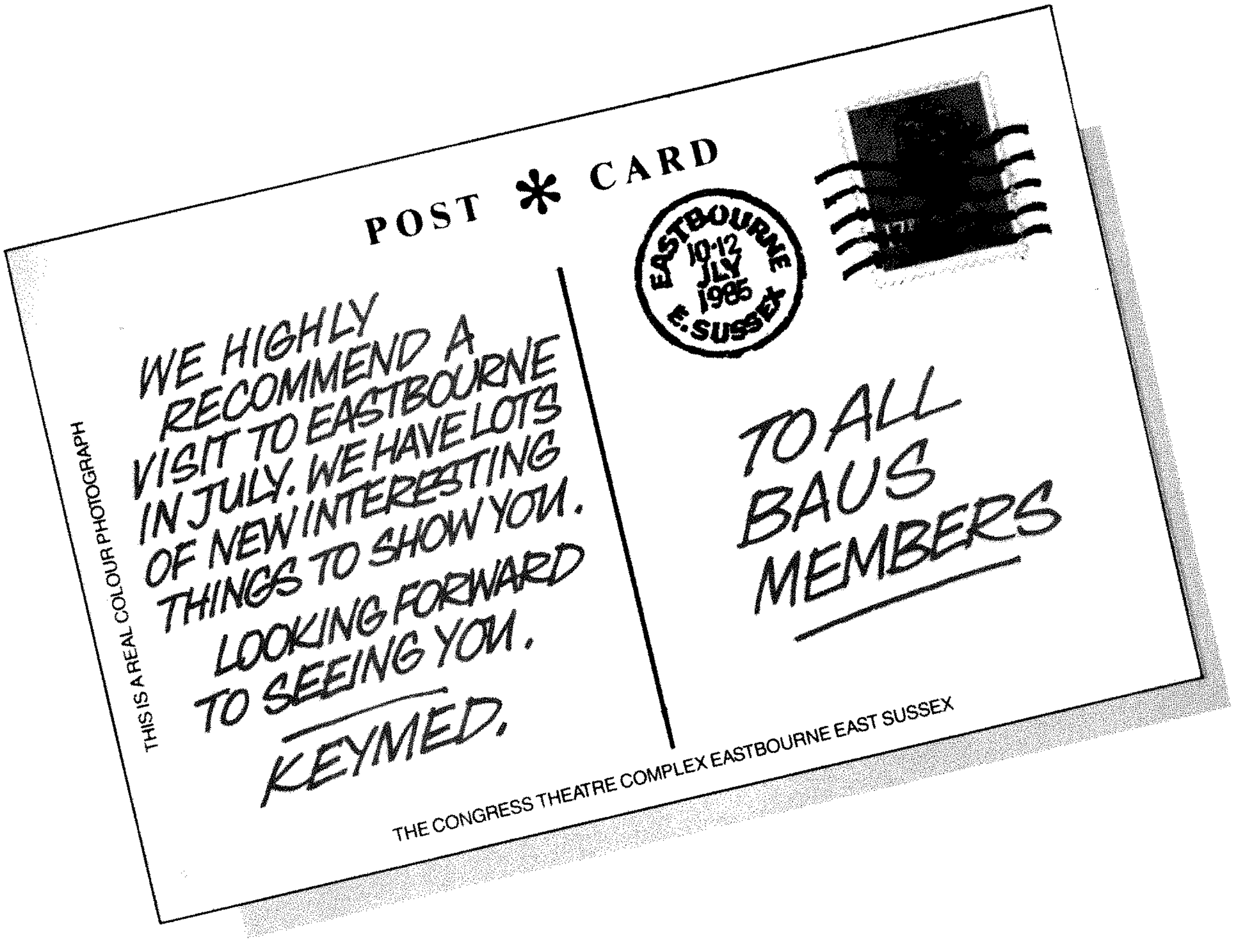

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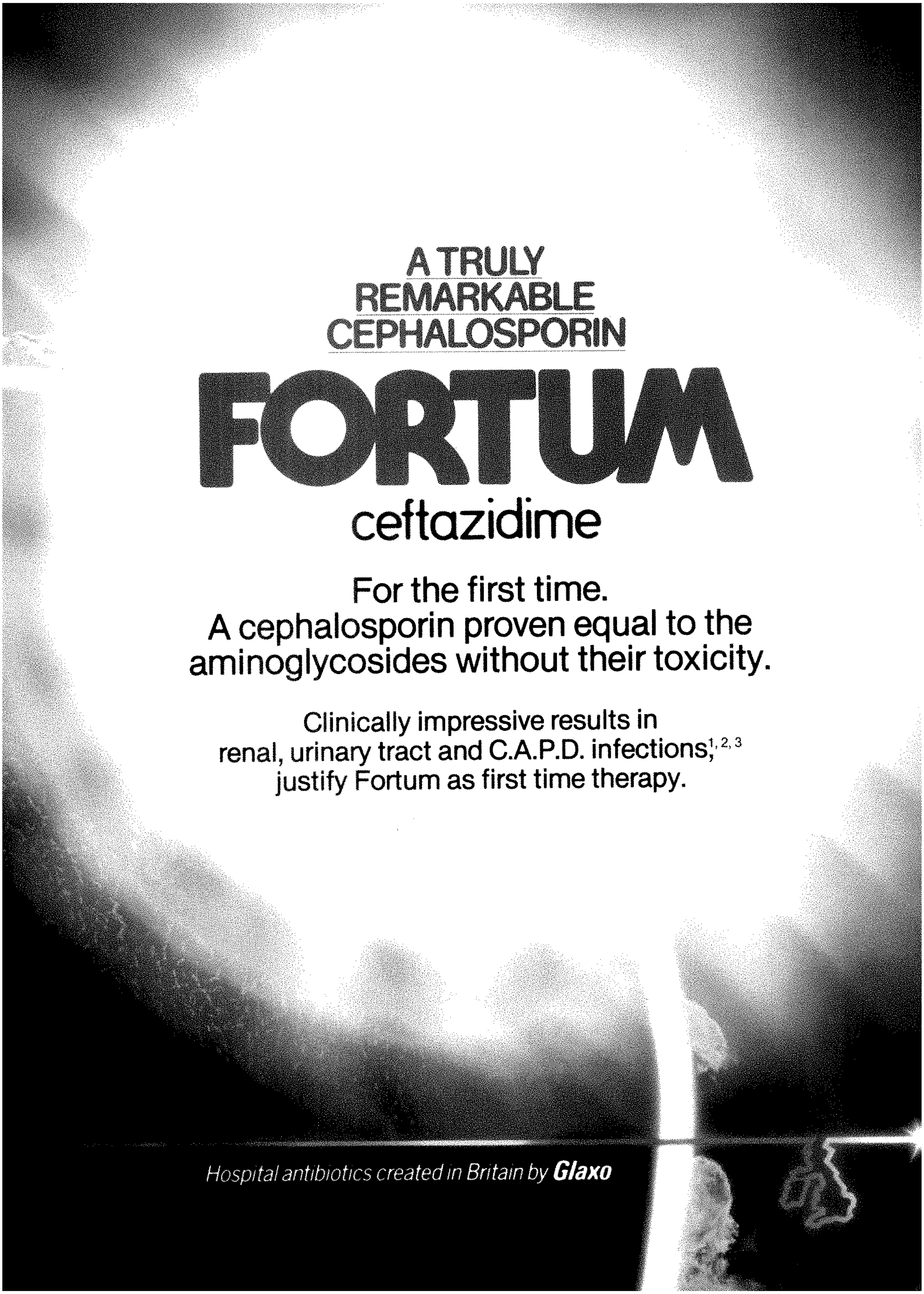

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1. Kawamura N. J of Antimicrob Chemother 1983; **12** (Supp. A): 65-70.
2. Cox C E. J of Antimicrob Chemother 1983; **12** (Supp. A): 47-52.
3. Bint A J, Constable J, Pattan K R, Constable F L. J of Antimicrob Chemother 1983; **12** (Supp. A): 115-121.

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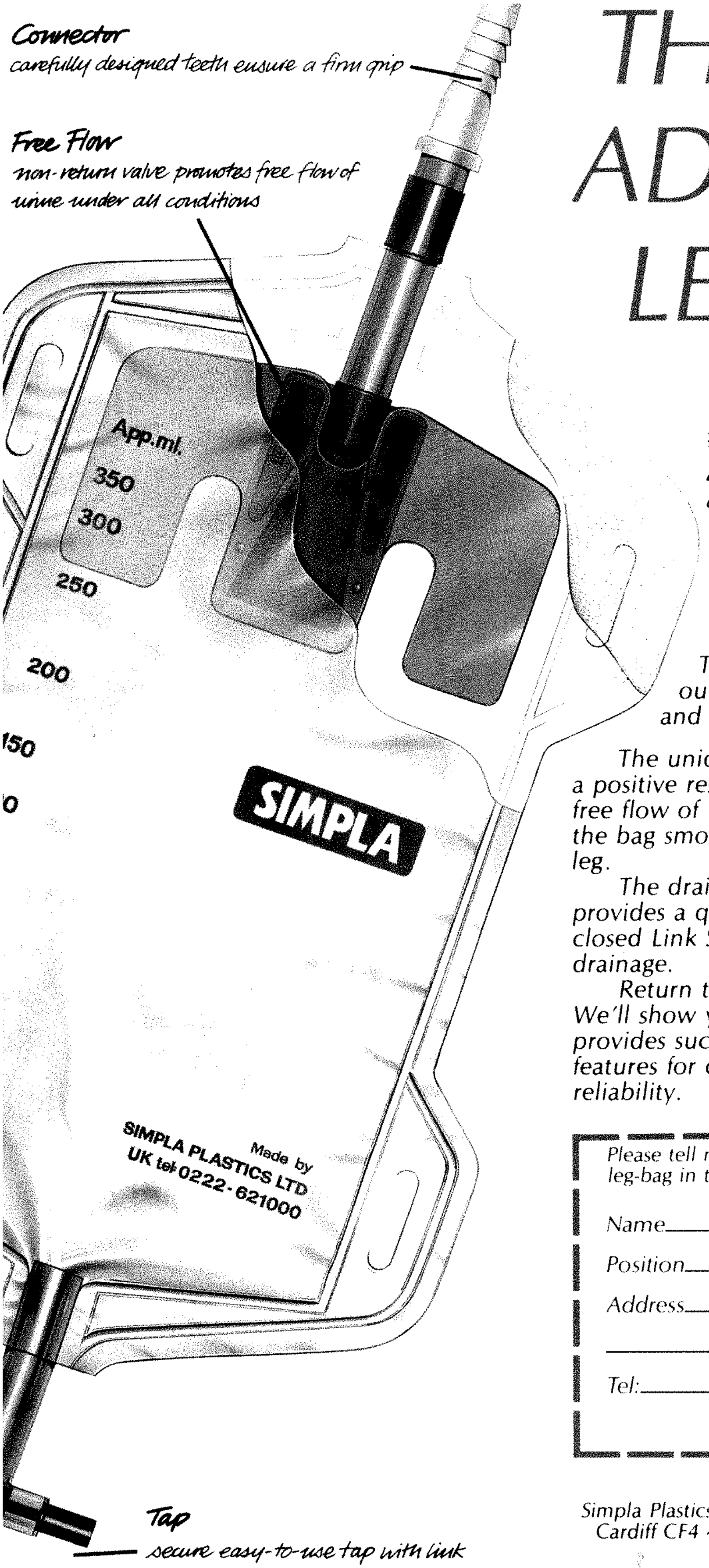
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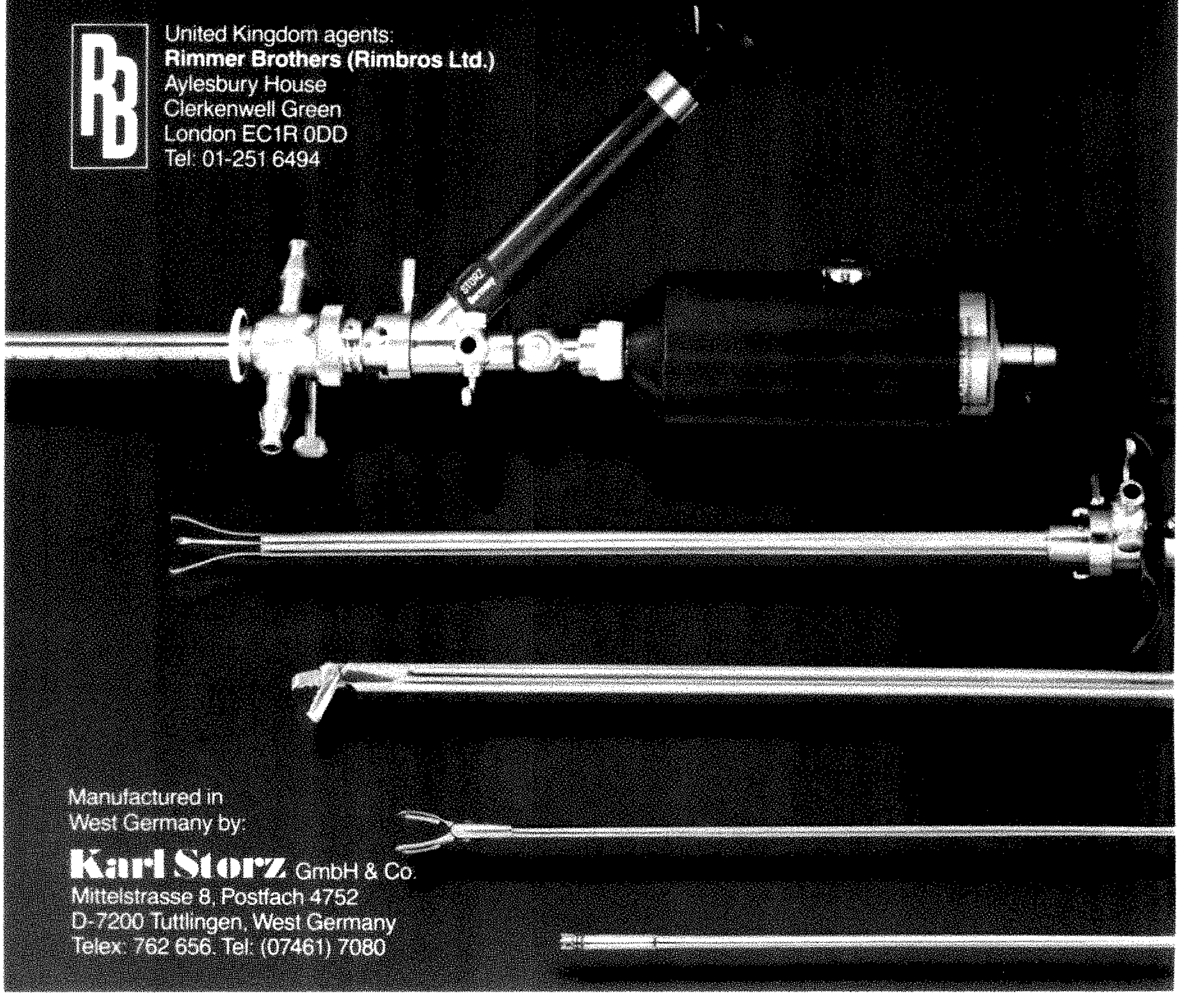

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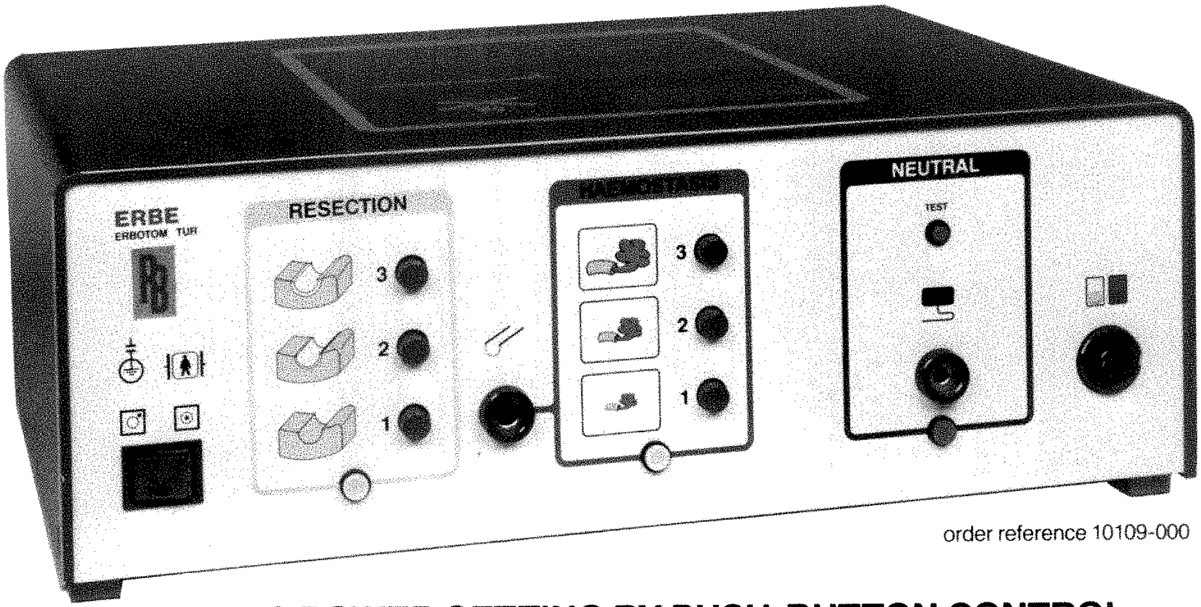

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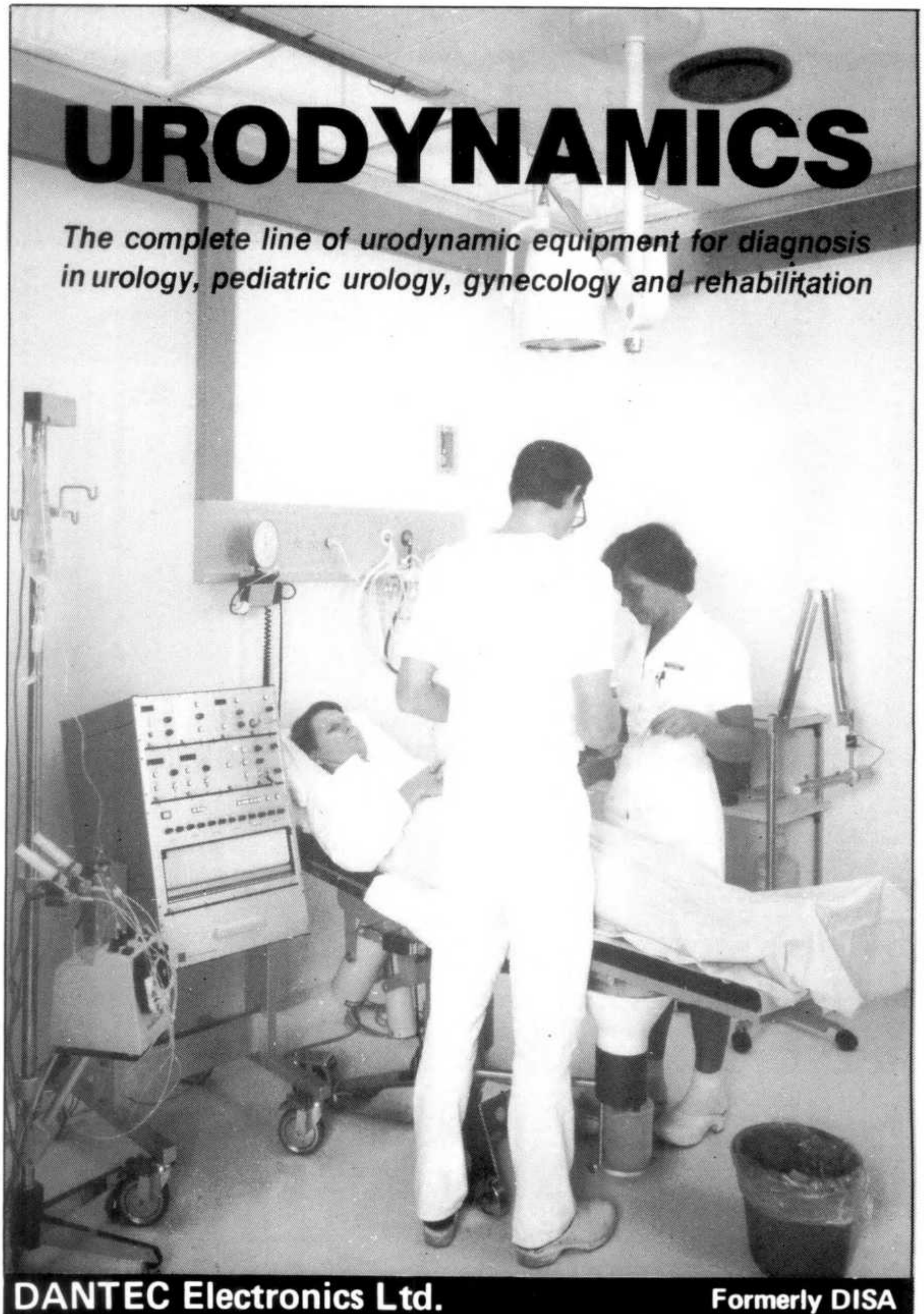

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REVIEW

The Changing Workload in Paediatric Urology

BARRY O'DONNELL and R. G. BUICK

Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Irish Republic

Summary—Almost 3000 (2969) paediatric urological procedures carried out by three paediatric surgeons over a 3-year period have been analysed. Almost half of the patients were managed as day cases. The content of the work has been examined and the implications for continuing patient care, surgical training and the desirable paediatric infrastructure noted. Inguinoscrotal operations, surgery for hypospadias and ureteric reimplant for vesicoureteric reflux are the commonest "open" operations.

Most paediatric urological procedures will continue to be done by a variety of surgeons of different specialities.

There are at least five recent books on paediatric urology. All quite properly give most space to the difficult and controversial problems. The larger texts go to some lengths to estimate the incidence of the various conditions but it is difficult to construct an overall picture of the subspeciality from the information provided. This is particularly true of the larger multi-author works.

A parallel development in recent years has been a trend to redefine the boundaries of work in various specialities and as the number of specialities increases the limitations of different subspecialities become more tightly delineated.

The concept of a pure paediatric urologist is a relatively recent one and it is doubtful if any were identifiable as such in 1960. The subspeciality of paediatric urology is not recognised by statute, specific training programmes or formal examinations in either Europe or North America but the number of such specialists is slowly increasing throughout the world. At the time of writing there are 4 full-time paediatric urologists in Great Britain and about 40 or 50 in the United States and Canada. Figures are necessarily imprecise because there are no subspecialist registers in either area. Even in the United States only a handful of centres have two pure paediatric urologists. This means that the useful concept of gentle, informal peer review is missing in most units. The impact on practices should not be underestimated.

Conditions differ widely. Perhaps the biggest difference is that there is central government control over the number and role of specialists in Great Britain and Ireland, whereas in the United States and Canada an adequately trained doctor may have a satisfactory professional life if he correctly identifies an academic institution or a community which requires his services.

There are three other groups of surgeons involved in the care of children's urological problems. Most urologists do some paediatric urology. Most paediatric surgeons in Great Britain and Ireland do a great deal of paediatric urology. As in adult urology, general surgeons do much of the open surgery in smaller hospitals. The growth in numbers of both those doing the work, and those who wish to do it, must be tempered by the volume and nature of the work that requires to be done.

Read at the 40th Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

Objectives of the present survey

Little has been done to investigate the actual workload—the how many of what. In this study we have attempted to carry out such a survey. It has been designed to show:

(i) What constitutes the workload.
(ii) The special features of the work.
(iii) The areas in which a trainee in either urology or paediatric surgery should have experience and develop special skills.
(iv) The areas of overlap with adult urology—particularly identifying those patients who need continuing care into adult life.
(v) The considerable infrastructure of personnel, and to a lesser extent equipment, required to deal with the special problems of paediatric urology.

The approach to the study was to take the workload of three paediatric surgeons, each with a particular interest in paediatric urology, working at a large (320 beds and cots) Dublin children's teaching hospital serving a densely populated urban community and acting as a referral centre for difficult problems from further afield. The unit has no monopoly locally or nationally but on available evidence it deals with the greatest number of patients in the subspeciality. Dublin has about 24,000 births a year.

The three surgeons dealt with almost 3000 (2969) paediatric urological procedures over the 3-year period 1981 to 1983 inclusive. These procedures constituted 38% of their total workload during this time. For our purpose we defined a procedure as an event which required a general anaesthetic and this definition underlines the necessity for a paediatrically orientated infrastructure.

What makes the workload?

Tables 1-9 show that the work was divided into

Table 1 Kidney Operations

Procedure	*Number*	*Comments*
Nephrectomy	39	Majority for small scarred kidneys with poor function
Partial nephrectomy	23	Majority for the upper pole of a duplex system (includes surgery for ureteroceles)
Nephrostomy (temporary)	18	Declining with invasive radiology
Pyeloplasty	45	Earlier diagnosis with ultrasound

Table 2 Bladder Operations

Procedure	*Number*	*Comments*
Cystostomy/vesicostomy	10	Mainly neuropathic bladders
Cystectomy	1	Exstrophic bladders not yet excised
Bladder exstrophy closures	11	Three new cases in 1981, 3 in 1982 and 5 in 1983
Bladder neck reconstruction	12	Bladder exstrophy/neuropathic
Exstrophy surgery	9	(Excluding primary closure)

Table 3 Reimplantation of Ureters

Number	*Indication*
112	Mostly for reflux (includes 17 for ureterovesical obstruction)

Table 4 Stone Operations

Procedure	*Number*	*Comments*
Pyelo/nephrolithotomy	24	10 in 1981, 8 in 1982 and 6 in 1983
Cystolithotomy	5	
Ureterolithotomy	0	

Table 5 Diversion and Augmentation

Procedure	*Number*	*Comments*
Colon conduits	9	Mainly exstrophy/spina bifida
Ileal conduit	1	Failed colon conduit
Colocystoplasty	2	Spina bifida

Table 6 Tumours

Procedure	*Number*
Wilms' tumour	13
Testicular tumour	2
Rhabdomyosarcoma of pelvis	2

(Excludes neuroblastoma of abdomen and pelvis)

Table 7 Urethral Surgery

Procedure	*Number*	*Comments*
Posterior urethral valves	7	Average 2-3 per year
Hypospadias operations	279	85% anterior hypospadias
Urethral fistular repair	38	All kinds of repair
Epispadias repair	2	Exludes exstrophy

Table 8 Inguinoscrotal Surgery

Procedure	*Number*	*Comments*
Orchiopexy	647 (22%)	Aged 1 year and upwards. (Laparoscopy for impalpable testes)
Hydrocele (patent processus vaginalis)	151 (5.1%)	
Scrotal exploration	134 (4.5%)	Torsion of appendix testis outnumbered torsion of testis

(Inguinal hernia (681) not included)

Table 9 Minor Operations (day care)

Procedure	*Number*	*Comments*
Cystoscopy	459 (15%)	Not for all UTI
Urethral dilatation (sounds)	206 (7%)	
Circumcision	571 (19%)	Uncommon under 2 years of age
Change of dressing	55	General anaesthesia required
Minor operations	79	

kidney operations (4.2%), bladder operations (1.4%), reimplant of ureters (3.7%), stone operations (1%), diversion and augmentation (0.4%), tumours (0.5%), urethral surgery (10.9%), inguinal/scrotal surgery (31%) and minor operations (day care) (46%).

Special features of the work

Open kidney and bladder operations constituted 11.2% of the procedures. These are the biggest operations. Most nephrectomies were for small scarred kidneys with poor function. Isotope renal scanning enabled us to identify kidneys with negligible function and these were routinely removed. Some of those nephrectomies were in patients who had had previous antireflux procedures. Many of the remnants were tiny dysplastic nubbins of tissue which may be difficult to find.

Most partial nephrectomies are for the removal of an upper pole of a duplex system. The diseased upper pole usually constitutes one third or less of the affected kidney. If there is a concomitant ureterocele the surgery for this is usually undertaken at the same sitting.

Temporary nephrostomy is now usually carried out by the radiologists under fluoroscopy, but a general anaesthetic is almost always required. A pyeloplasty in an infant under 1 year is one of the most demanding technical challenges in urology. A meticulous approach is required and the decisions about splinting and drainage put this operation in a different category from a similar operation in an older child. The antenatal diagnosis of the condition may put pressure on the surgeon for early intervention.

Cystostomy and vesicostomy are carried out almost exclusively for neuropathic bladders. However, we have used it on two occasions for the temporary management of posterior urethral valves in premature or sick infants. Cystectomy is rarely performed because we do not excise exstrophic bladders. Closure of bladder exstrophy is now advocated at about 1 month of age and meticulous technique using magnification has contributed to slowly improving results. Bladder neck reconstructions for exstrophy are carried out in almost all patients at a subsequent stage, usually 3 to 6 years of age. Even though we see only 3 to 5 exstrophies each year, which is a near national monopoly, there is almost always an exstrophy patient in the hospital having some procedure. One surgeon deals with all the exstrophy and epispadias children.

Reimplantation of ureters is mostly performed for vesicoureteric reflux. The majority of the patients who were having antireflux surgery had a Cohen transtrigonal reimplant, though the Leadbetter-Politano operation is still sometimes used by all of us in certain circumstances. Surgery for vesicoureteric reflux constitutes the commonest open operation and if an endoscopic approach to this condition becomes successful in a significant proportion of cases, it will have a noticeable effect on the workload of paediatric urologists. Seventeen patients had reimplantation for ureterovesical obstruction and most of these had a short length of tapering.

Stone operations have become less common. In the last year of this survey (1983) we saw only 7 cases. This is our lowest number for more than 20 years. Few calculi in children are suitable for percutaneous methods as most patients are under 8 years of age. We have no access to a lithotriptor at present.

Few diversions have been performed in this unit over the years; only 6 ileal conduit loops were performed between 1959 and 1974. The favoured diversion at the present time is colon conduit and this has been employed in 9 patients, mainly for exstrophy and spina bifida. We have not so far been enthusiastic about bladder augmentation.

The management of Wilms' tumour used to be entirely surgical but now has become primarily an oncological responsibility in which the surgeon plays a part. There are at least six varieties of Wilms' tumour and this has to be multiplied by the five groups to provide the exact staging which is a vital part of the treatment. The results of management in Wilms' tumour have improved greatly in recent years following the introduction of effective chemotherapy and the appearance of paediatric oncologists. The timing and nature of the surgery is usually decided following extensive assessment and possibly prior therapy. Having seen these schemes in action we would not now like to treat a Wilms' tumour without the help of a paediatric oncologist. We no longer live in the days of "let not the sun go down on a Wilms' tumour".

Urethral surgery is dominated by operations for hypospadias; 85% of these are for anterior hypospadias and the most commonly used procedures are Duckett's MAGPI and the Van de Muelen. Several different procedures are used for the more proximal problems. Fistula formation in the anterior hypospadias is rare but does occur in the more proximal and difficult problems. The fistula rate is declining.

Posterior urethral valves are dealt with by transurethral fulguration if the patient is big enough to take the urethroscope. Otherwise a vesicostomy is performed.

Orchiopexy is the single commonest urological operation. The majority of boys were over 4 years of age but there is a tendency to perform the elective procedure between 2 and 4 years. Laparoscopy is used routinely for bilateral impalpable testes and sometimes in unilateral impalpable testes. It has been a most useful diagnostic tool. A high incision is used for the impalpable testis and fixation is usually achieved by the dartos pouch method. Surgery for hydrocele is the division of the patent processus vaginalis; classical inversion or excision procedures as practised in adults are not used.

Cystoscopy is not routinely performed for each child with a urinary tract infection and the average of three cystoscopies a week over the period under review may appear small but this is an informally agreed policy. Circumcision is not commonly carried out on children under the age of 2 years.

Day care is the routine for cystoscopy, circumcision, change of dressings, urethral dilatation, hydrocele and other minor operations. It is used increasingly for anterior hypospadias and orchiopexy. As the average age of patients falls the unit requires more cots and fewer beds. This has considerable implications for anaesthesia and nursing services, for the training of surgical residents and for all forms of investigation.

Consultation work

The spectrum of consultations is completely different from that found in adult work. Perhaps the commonest problem is the continuing conservative management of neuropathic bladders. The hospital has the largest spina bifida unit in the country. Many patients are managed by intermittent catheterisation or intermittent self-catheterisation and a specially trained nurse is employed to look after them. There are also consultations in the management of associated urological abnormalities such as those found in imperforate anus, congenital heart disease and chromosomal abnormalities. Approximately one-fifth of patients with vesicoureteric reflux have operative treatment and there is continuing assessment with the paediatricians of the patients who are managed conservatively. Intersex problems are neonatal emergencies and are treated as such.

Areas in which a trainee should develop special skills

It is clear from this survey that the bulk of the operative work in paediatric urology concerns orchiopexy and hypospadias. The problem of undescended testes contains a great number of variations and the approach changes with the exact nature of the problem. The full spectrum of variants can only be appreciated where there is a substantial volume of operative work.

Until some 15 years ago most hypospadias operations were carried out by plastic surgeons but now both the younger generation of urologists and most paediatric surgeons take an interest in this subject. It requires a meticulous approach, frequently using different techniques, for the many variants of the condition.

With an increasing number of younger patients the use of fine materials, and the advisability of magnification inherent in their use, become a necessary part of training. It is doubtful if all of those interested in paediatric urology require exposure to microsurgery but its use is certainly good for technique in many of the problems in this age group.

Endoscopy presents fewer challenges and less variation in the paediatric age group and it is our experience that residents with a general surgical training can quickly learn the technique and interpret the relatively small range of abnormal findings.

An orderly approach to investigation is important. The patient with urinary tract infection may well come to a surgeon having had an intravenous urogram, blood chemistry and possibly a renal scan, but not the unpopular but often necessary micturating cystourethrogram.

Skin incisions should be closed with subcuticular sutures in virtually every condition, whether the wound is clean or infected.

A trainee fresh from adult urology might well express surprise at the paucity of transurethral procedures. Posterior urethral valves are almost the only transurethral operations. Many trainees expect posterior urethral valves and Wilms' tumours to figure prominently in the operating lists but our data, which show 2 or 3 cases of urethral valves and 4 or 5 cases of Wilms' tumour each year, have remained fairly steady and represent an average intake for most units in these islands.

Areas of overlap with adult urology

It surprises our colleagues and ourselves how few patients require eventual transfer to adult units. Patients with diversions, neuropathic bladders (many of whom have not had any major surgery), bladder exstrophy and severely scarred kidneys constitute the bulk of eventual referrals. We do not routinely transfer to adult units the patients who have had orchiopexy, successful hypospadias repairs, nephrectomy for pyelonephritis or single operations for stone. Most stones in childhood do not recur and most patients have been followed up for at least 10 years at the time of discharge from the paediatric unit.

It may be remarked that surgeons as well as patients grow old. A youthful paediatric urologist or paediatric surgeon would do well to remain silent if an elder of the urological establishment criticises the fragmentation of urology into age groups on the basis that he, the adult urologist, is in a better position to follow the patient throughout life.

Many paediatric urologists do not have a significant adult appointment but tend rather to follow their patients through to 16 or 18 years of age at their principal place of work.

Paediatric infrastructure

Large numbers of patients are most likely to be treated in a large paediatric unit but this does not mean that a high standard of care cannot be achieved outside it. We feel it appropriate to point out features in our own unit by which we try to make it efficient, effective and humane.

Day care is used for almost half of all procedures requiring a general anaesthetic. We have an informal day care unit with a varying number of cots and beds to juggle with as the need arises. Day care puts a premium on all aspects of anaesthesia and cannot succeed without the expertise and enthusiastic co-operation of this department.

Nursing of small infants, particularly with respect to catheters and other tubing following operations, requires great vigilance.

One paediatrician in our hospital has a special Urinary Tract Infection Clinic. He also deals with most cases of enuresis. As part of his service there is a Urinary Tract Infection Unit under the care of a State Registered Nurse. Postal surveillance of urinary tract infection using dip slides and "Microstix" has been effective. This part of the service grew out of a large hospital-based school screen programme for bacteriuria in the locality.

Imaging requirements include good quality intravenous urograms in small patients, acceptable micturating cystourethrograms in the uncooperative child and high resolution ultrasound examinations. One of the three radiologists has taken a particular interest in percutaneous work.

In the operating theatre most special instruments are scaled-down versions of adult prototypes. We have cystoscopes of varying sizes from 8 to 17F and a 14F resectoscope. Transurethral biopsy is a rare operation even in the large oncology unit we serve. An instrument repair and replacement service is vital. A wide variety of catheters and stents, including Fogarty catheters, is kept available. A range of these disposables is required for patients of all ages.

Epilogue

Most of the procedures named in the foregoing survey can be and are carried out in many hospitals by general and plastic surgeons as well as by the three categories of surgeon outlined. As in adult urology, it is likely that these practices will continue. Responsible attitudes towards the referral of uncommon and difficult problems prevail. The caring doctor will balance a journey or a series of journeys to an appropriate unit against the possibility of prolonged hospitalisation or residual disability.

It may appear to some that much of paediatric urology resembles paediatric surgery almost more than it does adult urology. This is an observation and not a strident statement of territorial claim.

In most areas both urologists and paediatric surgeons will continue to compete in the treatment of the problem cases. The increase in the numbers of paediatric urologists will be slow.

Acknowledgement

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The Authors

Barry O'Donnell, MCh, FRCS, FRCSI, Consultant Paediatric Surgeon.

R G Buick, FRCSE, formerly Senior Registrar in Paediatric Surgery. Now Consultant Paediatric Surgeon, The Children's Hospital, Birmingham.

Requests for reprints to· Barry O'Donnell, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Irish Republic.

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A Computer Program for Urology

M. B. ROSE, P. A. GEORGHIADES and W. B. DOWSLAND

Department of Urology, Morriston Hospital and Department of Management Science and Statistics, University College of Swansea, Swansea

Summary—Modern information technology offers new opportunities for the storage and manipulation of clinical data within hospital departments. We have designed and put into use a microcomputer system for urology. Its basic structure and main functions are described.

The use of computers to store information and to help make decisions is becoming commonplace. This is partly because micro-computers are now relatively cheap and can, with suitable programs, be used with ease by non-experts. Medicine in general has been slow to make use of this new technology. Administrative tasks, such as maintaining a master index of patients, are gradually being computerised. Clinical computing techniques are on trial in general practice (Turner *et al.*, 1980) but there are few clinical doctors who use computers regularly in their work. Some hospital departments are using computers to produce clinical records (Clarkson *et al.*, 1982) or as aids to diagnosis (De Dombal *et al.*, 1974). In urology, Wickham *et al.* (1975) described a system to record and analyse clinical data on a mainframe computer, which required the co-operation of a computer department. Glen (1983) has indicated some possible uses of microcomputers in urology. We have designed a microcomputer program specifically for use by clinicians and secretarial staff and have put it into use in a urology department.

Aims

Every clinical department needs to know details of the patients it treats, for administrative, research and audit purposes. Clinical details are notoriously difficult to extract from hospital records: relevant information may be missing or hidden in a mass of illegible notes. Hospital Activity Analysis provides only limited information and its accuracy depends on the source of its information.

Over the past 7 years, diagnoses and treatments have been recorded on card index for every in-patient admission to the urology department in Swansea. Comprehensive details about all patients with transitional cell carcinoma have also been kept on punched cards. With approximately 700 admissions a year, under 2 consultants, including 150 cystoscopies for bladder tumour, these cards were becoming too many for easy analysis. The obvious solution was to computerise the information.

In addition to requiring the clinical data, we were concerned that bladder tumour patients were sometimes being lost to follow-up. Also, we hoped to find out if the rate of recurrence of bladder tumours could be predicted, to see whether the frequency of cystoscopies could be reduced without putting patients at risk.

When we started the project in 1981 there were no computer programs available which would help with these tasks. We therefore designed a system from first principles, having first analysed how the information we wanted was already being recorded and used.

Equipment

The programs were developed on a 64K, Z80, 8-bit microcomputer using a twin floppy disc drive and

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the CP/M operating system. The system is now running on a Comcen Crystal 8 microcomputer with a 10 M-byte Winchester disc drive, with floppy disc back-up, and a dot matrix printer. Space is available for about 15,000 admissions.

Functions

The program was designed to store and manipulate clinical data about in-patients. Patients with transitional cell carcinoma have again been selected for study in particular detail. The program is an interactive one; the user is at each stage guided by instructions appearing on the screen.

There are 6 basic subroutines.

1. Input

For a patient new to the system, administrative details are first entered (Table 1). A previously entered patient is identified by the hospital number and the date of birth. For each admission we chose to record the date and up to 3 diagnoses and 3 operations (using our own code for diagnoses and the "International Codes of Operations") (Table 2). If the patient is treated for transitional cell carcinoma, details about the findings and treatment are entered (Table 3). Comments in free text can also be added, although these cannot be analysed. Inbuilt checks ensure that impossible answers are not given, *e.g.* a date such as 30th of February. About 40 records can be entered per hour.

Table 1 Administrative Details Recorded for each Patient

Hospital number
Surname
First name
Initials
Sex
Date of birth
Address
Hospital of initial diagnosis
Consultant

Table 2 Clinical Details Recorded for each Admission (Excluding Admissions Recorded under Table 3)

Date of admission
Type of admission (routine, emergency)
Diagnoses 1, 2, 3
Treatment 1, 2, 3
Prostatic weight (if applicable)
Smoking habits

Table 3 Clinical Details Recorded for each Admission for all Bladder Tumours, and Transitional Cell Tumours Elsewhere

Date of cystoscopy

Findings
Site of tumour (*e.g.* bladder, urethra, ureter, kidney)
Number of tumours
Average size of tumours
Appearance of tumour (moss, papillary, mixed, solid)
EUA (no mass, induration, mobile/fixed mass)
Pathology of worst tumour (well/moderately/poorly differentiated, anaplastic)
Histological type (transitional cell, adenocarcinoma, squamous, other)
Invasiveness (*in situ*, stromal, superficial/deep muscle, fixed)

Treatment
Surgery (none, biopsy, fulguration, TUR, suprapubic cystectomy, partial/total cystectomy)
Radiotherapy (none, interstitial, external)
Chemotherapy (none, intravesical, systemic); number of doses

Site of other tumours
Bladder, kidney, ureter, urethra

Other
Duration of cystoscopy
Date of next cystoscopy
Smoking habits

2. Output

By using the patient's hospital number the previously recorded details about any admission can be obtained and printed in various forms. The output is linked to a word processing program where it provides the basic administrative and clinical details, to which further text can be added to produce a discharge letter. An inbuilt diagnostic and operations dictionary converts coded entries into text.

3. Selection

Patients can be selected on the basis of up to five criteria taken from any of the items stored (Tables 1, 2 and 3); for example, diagnosis: transitional cell carcinoma; operation: cystectomy; sex: female. The number of selected patients is given and up to five of the recorded items can be displayed for each one. The selected group can then be sorted into the order required by the user.

This program permits a list of bladder tumour patients due for a check cystoscopy by any given date to be obtained.

Table 4 Numbers of Prostatectomies Performed by One Surgeon (August 1977-December 1983)

	Year						
Operation	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*
TUP	51	116	105	103	109	94	105
RPP	8	14	12	3	9	0	4
TVP	1	0	0	1	1	0	0
Total	60	130	117	107	119	94	109

TUP—Transurethral prostatectomy
RPP—Retropubic prostatectomy
TVP—Transvesical prostatectomy

4. Analysis

The details recorded for all admissions (including cystoscopies for bladder tumours) can be analysed by year, patient's age or consultant. The number of different operations or diagnoses can be found as well as, for example, the proportion of emergency to routine admissions, the areas from which selected patients come, or the age and sex of patients admitted in different years (Table 4).

5. Trends

Any two numeric items of information about one or more patients which have been recorded on a number of admissions can be plotted against each other on a graph, *e.g.* number of tumours found against time since last cystoscopy (Fig.).

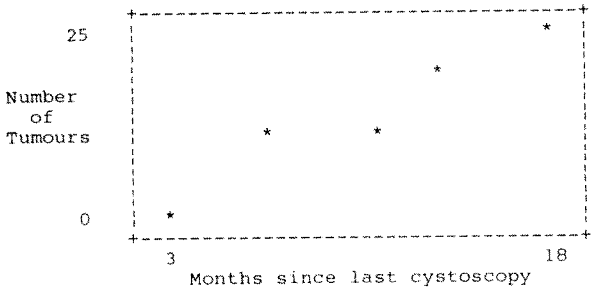

Fig. Graph for an individual patient; number of bladder tumours found at cystoscopy against time since last cystoscopy.

6. Recall

This is an experimental program which suggests, for each bladder tumour patient whose check cystoscopy details are entered, a date for the next cystoscopy. The time interval is based on the number, size, stage and grade of tumours found, using previously defined logic embedded in the program. If the suggested date is not accepted, then the interval suggested next time, on the basis of the same criteria, is adjusted; *i.e.* the computer "learns". After the system has been in use for some time, we intend to find out whether the doctor or computer has made a better estimate of the timing of the next cystoscopy, judging by the duration and outcome of that operation. We assume the duration should be about 30 min—less may be a waste of everyone's time, more could increase the risk to the patient.

Uses

Using this system and without the hospital notes it is possible to:

(i) Find out if a newly arrived patient has been an in-patient in the department before. If so, previous diagnoses and treatments will be available, together with basic administrative information.
(ii) Obtain full details of a patient's previous investigation and treatment for bladder tumours.
(iii) Find out how many patients have been admitted with any particular diagnosis or had any operation, and obtain details of those patients.
(iv) Establish which patients are due for their next cystoscopy for bladder tumour—independently of hospital routines.
(v) Analyse diagnoses, operations, *etc*, by year, age group or consultant.
(vi) Look for any number of possible correlations between various aspects of transitional cell carcinoma.
(vii) Investigate the best timing of repeated cystoscopies for bladder tumours.
(viii) Produce hospital summaries or letters giving administrative and clinical details, to which more can be added as needed.

Discussion

This system is easy to use. Data can be entered by secretaries and the various programs used after brief training and without special computer knowledge. It is independent of hospital records. With its use, the workload of the department can be quickly measured and the initial stages of audit or research are greatly speeded up. Patients needing follow-up are less likely to get lost. Detailed analyses of subgroups of patients can be made and a project involving a large number of patients made possible. Other studies could be designed to use the information available.

The system is constructed to be adaptable. The data to be stored are defined by the user beforehand and need not be as shown in the Tables; in fact the system could be used for a speciality other than urology. Up to six other subgroups could be studied in detail besides bladder tumour patients. New ways of analysing the data can be introduced at any time.

When this system was being developed, only 8-bit machines were available. Faster working and greater memory can be obtained with 16-bit computers and if we were starting today we would probably use them.

We know of no commercially available program for recording urological data, although programs for similar jobs exist in other specialities. Sophisticated general use database systems exist and could be adapted but would probably require some programming knowledge. Our system has been designed specifically for use by non-experts in order to take over and expand the method of recording clinical information that is already in use. We present this brief account in order to show how, with present-day technology, it is possible to design a simple and efficient method for the storage and retrieval of clinical information within a hospital department.

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The Authors

M. B Rose, FRCS, MChir, Consultant Urologist, Morriston Hospital.

P. A Georghiades, MSc, Research Student, Department of Management Science and Statistics, University College of Swansea.

W B Dowsland, PhD, MBIM, Lecturer, Department of Management Science and Statistics, University College of Swansea

Requests for reprints to· M. B. Rose, Department of Urology, Morriston Hospital, Morriston, Swansea SA6 6NL.

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Xanthogranulomatous Pyelonephritis in Childhood

F. KIERCE, R. CARROLL and E. J. GUINEY

Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Irish Republic

Summary—Eleven children with xanthogranulomatous pyelonephritis are reported. The left side was affected in all patients. It is suggested that the diagnosis can be made pre-operatively. The condition is characterised by the fact that it is always unilateral and that renal calculi are found in a kidney with gross impairment of function; associated anaemia, leucocytosis and raised ESR are also present. The cause is unclear, but an obstructive element with infection is usually found.

Xanthogranulomatous pyelonephritis (XGP) first described by Schlagenhaufer in 1916, accounts for 6 per 1000 of surgically proven cases of chronic pyelonephritis (Malek *et al.*, 1972). Women are affected more often than men, usually from 40 years onwards, and the disease has a peak incidence in the sixth and seventh decades (Malek and Elder, 1974). Up to 1982 only single cases were described in children and in all instances these were female (Avnet *et al.*, 1963; Friedenberg and Spjut, 1963; Black and Ragsdale, 1968; Lackner *et al.*, 1969; Graivier and Vargas, 1972; Gingell *et al.*, 1973; Bagley *et al.*, 1977; Schulman and Denis, 1977; Shapiro *et al.*, 1978; Moller and Kristensen 1980; Yazaki *et al.*, 1982). In that year five childhood cases, three boys and two girls, were reported by Watson *et al.* (1982).

Patients

The present series of 11 affected children is the largest in the literature to date. There were 7 female and 4 male patients. The children presented between 1967 and 1983 and their ages ranged from 2 to 11 years. For a condition which when diagnosed is evidently of long duration in evolution, the presenting symptoms and signs were of remarkably short duration. Also remarkable is the fact that there was no history of previous urinary tract infection in these children, although such a history is common in affected adults. One patient presented with a non-tender palpable mass in the left loin and a proposed diagnosis of Wilms' tumour. On examination a further five patients had a palpable mass in the left renal area. One patient presented with intestinal obstruction and generalised abdominal tenderness. Another patient had evidence of a fluid collection in the left pleural space which was in fact an empyema.

Amongst the original clinical diagnoses were: osteomyelitis; leukaemia with splenomegaly; Wilms' tumour twice with pulmonary metastasis in one of these two patients; intestinal obstruction; failure to thrive; hepatosplenomegaly; dysuria/frequency and perinephric abscess (twice). In view of these protean presentations, symptoms and diagnoses, it is not surprising that XGP is frequently a post-operative and pathohistological diagnosis rather than pre-operative and clinical.

Radiological examination showed a non-functioning left kidney in 9 patients and a poorly functioning left kidney in 2. Renal calculi were evident in 10 of the 11 cases.

In 6 patients the urine was sterile but pus was present in 4 of the 6. *Escherichia coli* grew in 2 patients and *Proteus* in the remaining 3.

Only 4 of the 11 children had a pyrexia at the time of presentation. In 4 patients compensatory hypertrophy of the unaffected kidney was noted on intravenous urography.

Only 2 patients had a haemoglobin exceeding 110 g/l; 5 were severely anaemic. The ESR was raised

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Read at the 40th Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

in the 5 patients in whom it was done, and 8 had a polymorphonuclear leucocytosis.

At operation the kidney was enlarged in 9 patients and densely adherent to the surrounding tissues. In 2 cases the kidney was adherent to the descending colon and in another the small intestine was adherent to an abscess in the lower pole of the kidney, causing intestinal obstruction. In 3 cases perinephric abscesses were present. Nephrectomy was performed in all cases. At operation we recommend a more anterolateral large incision rather than the standard loin renal approach. A characteristic finding is dense adherence of the diseased kidney to the surrounding structures. It is virtually impossible to do the necessary nephrectomy without opening the peritoneum and indeed it is wiser to do so, since the small bowel in one instance and the large bowel in another two cases was adherent to the kidney and had to be separated by sharp dissection and with care. Adherence to the diaphragm is also usual and in one instance this resulted in development of an empyema. The adrenal gland is also involved in the inflammatory mass and an effort should be made to preserve it, although this may not always be possible.

Pathological Details

In all instances the surfaces of the kidneys showed marked scarring and in the most severe cases the parenchyma of the kidney was replaced by pus-filled cystic spaces with a marked yellowish tinge to the parenchyma at the edge of the pus-filled areas (Fig. 1). In other cases the renal parenchyma beginning at the medulla was replaced by streaks of yellowish material. In 10 of the 11 cases the presence of calculi was confirmed. In only one instance was there clear evidence of pelviureteric obstruction.

All of the kidneys showed evidence of hydronephrosis. Histological examination showed central collections of polymorphonuclear leucocytes surrounded by fat-filled macrophages and multinucleated giant cells (Figs 2 and 3). Some of the giant cells were adjacent to cholesterol clefts. Lymphocytes and plasma cells were also present. The areas of inflammation were surrounded by fibrous tissue. The remainder of the kidney showed evidence of chronic pyelonephritis (Fig. 4).

Radiological Appearances

The appearance of a number of stones within the renal substance is usually seen on straight film of the abdomen. In addition there may be stippled areas of calcification. The renal outline is not usually well seen and there may be evidence of contralateral compensatory hypertrophy.

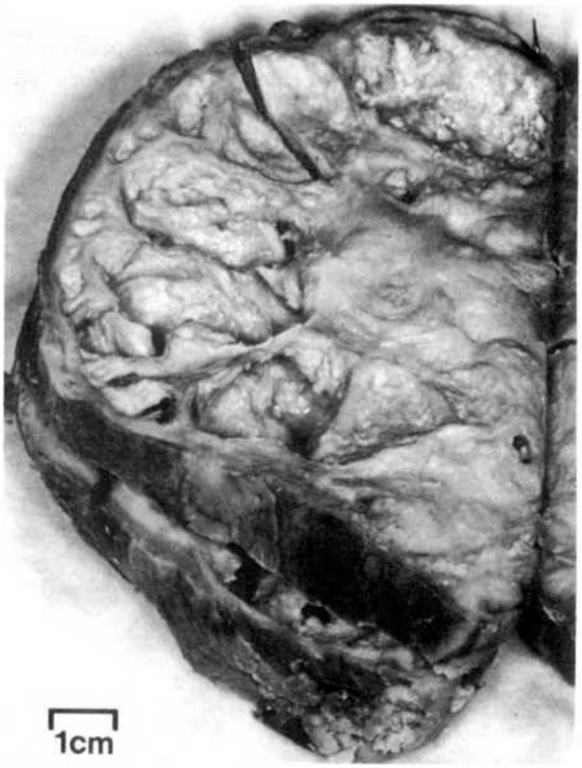

Fig. 1 Cut surface of kidney showing cysts containing soft material.

Discussion

These 11 children had severe unilateral renal disease, necessitating nephrectomy. The operative findings of dense adherence to adjacent structures and the macroscopic and microscopic appearance of the kidney all strongly support the belief that the disease process had developed over years rather than months. In this context it is surprising that there were so few urinary symptoms. The absence of these symptoms and the finding of sterile urine can be misleading and result in errors of diagnosis and management. We believe that the presentation of this condition is sufficiently characteristic to enable a confident diagnosis to be made on a pre-operative clinical basis. In the last 4 patients of this series the correct pre-operative diagnosis was made. The characteristics of the condition are:

(i) It is always unilateral.
(ii) There is absent or grossly impaired renal function on the involved side.

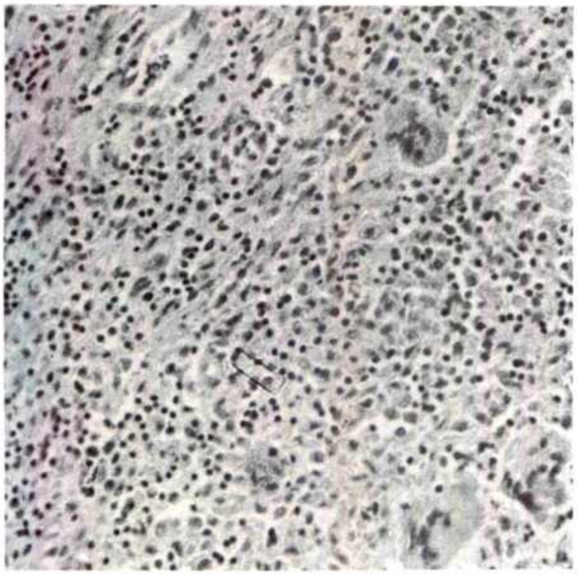

Fig. 2 Inflammatory cells and multinucleated giant cells (H and E × 80).

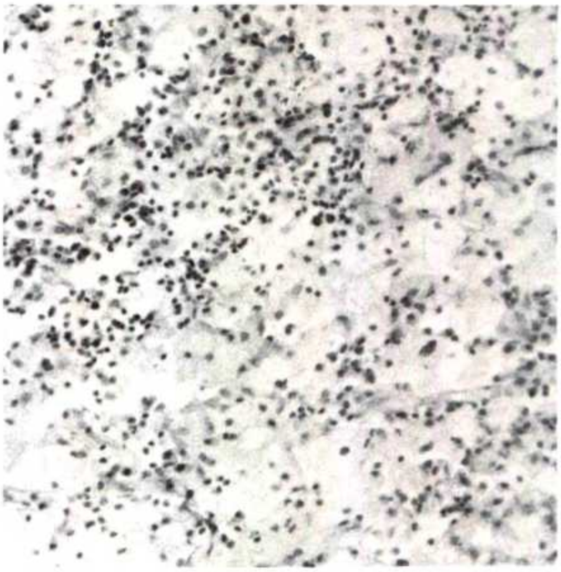

Fig. 3 Macrophages containing pale staining lipid (H and E × 80).

(iii) Large, frequently numerous renal calculi are present.

(iv) Anaemia, raised ESR and leucocytosis are commonly present.

The characteristics may not all be present in each case; for example, there was no stone in one of our series, but a combination of most of these findings should suggest the diagnosis to the prepared mind. As so often occurs with relatively rare conditions, to think of the diagnosis is to make it.

In this series the remarkable finding that the left kidney was affected in all instances could possibly be dismissed as a statistical maverick, particularly as the literature referring to adults states that there is no predilection for either side to be involved. Watson *et al.* (1982), who refer to 50 previously reported childhood cases and report 5 additional ones, concur with this view. However, statistical analysis of our series stated that it was highly significant to have a single side involvement in 11 consecutive cases. The statistician stated: "Using the binomial distribution, the 99% confidence interval for the percentage of left side affected kidneys is from 0 to 38%, showing a highly significant departure from the expected rate of 50%".

In view of this we have to challenge the statement that in children there is no predilection for a particular side (Watson *et al.*, 1982).

With regard to possible causes, obstruction with associated infection was the dominant feature in

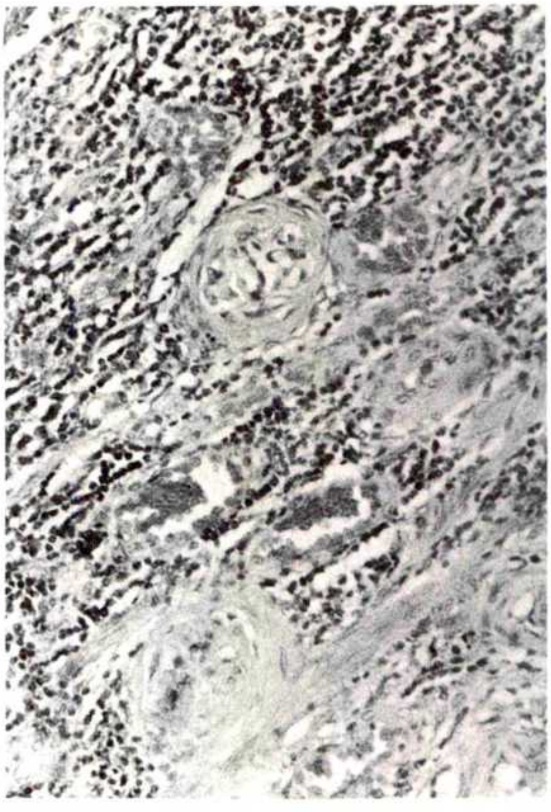

Fig. 4 Histological changes of chronic pyelonephritis (H and E × 80).

that all kidneys showed evidence of hydronephrosis and contained pus, as well as the microscopic evidence of occult and chronic infection. However, positive evidence of obstruction was found in only one of the cases reported. The calculi were an obstructing agent in the remaining 10 kidneys. Other suggested aetiological factors do not stand up to critical appraisal. For instance, ineffective antibiotic therapy of a relatively benign chronic urinary infection can hardly be responsible since XGP was described long before antibodies were first discovered. No case of bilateral XGP has been reported; the condition therefore is unilateral and this would not be so if the patient had abnormal lipid metabolism, another aetiological factor that has been suggested.

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The Authors

F Kierce, MB, BCh, BAO, Registrar, Department of Pathology, Our Lady's Hospital for Sick Children and University College, Dublin.

R Carroll, MD, FRCPI, FRCPath, Consultant Pathologist, Our Lady's Hospital for Sick Children and University College, Dublin.

E J Guiney, MCh, FRCS, FRCSI, Consultant Paediatric Surgeon and Professor of Paediatric Research, Our Lady's Hospital for Sick Children and University College, Dublin

Requests for reprints to. E J Guiney, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Irish Republic

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The Effect of Trimethoprim on Serum Creatinine

J. KASTRUP, P. PETERSEN, R. BARTRAM and J. M. HANSEN

Department of Internal Medicine and Endocrinology· Department of Clinical Chemistry, Herlev University Hospital, Herlev, Denmark

Summary—The influence of trimethoprim on renal function has been investigated in two groups of volunteers, both without a history of either acute or chronic urinary tract disease. All had normal serum creatinine. They were treated with trimethoprim 200 mg bd for 14 days. In group A (median age 78 years), serum creatinine increased significantly from median 89 to 134 μmol/l ($P < 0.01$) during the first week and returned to normal 1 week after termination of treatment to median 90 μmol/l ($P < 0.02$). After 1 week's treatment in group B (median age 29 years), serum creatinine had increased significantly from median 87 to 107 μmol/l ($P < 0.05$), remained stable in the second week and returned to the pre-treatment level 1 week after cessation of treatment: 87 μmol/l ($P < 0.05$). The glomerular filtration rate determined by ^{51}Cr-EDTA clearance did not change. There was a significant decrease in the 24-h endogenous creatinine clearance after 14 days' treatment from 111 to 87 ml/min/1.73 m^2 ($P < 0.05$). Our results are consistent with an age-independent reversible trimethoprim-induced inhibition of the tubular secretion of creatinine.

There is some controversy about the effect of co-trimoxazole (trimethoprim—sulfamethoxazole) on renal function. Some authors have reported a deterioration (Kalowski *et al.*, 1973; Horn and Cottier, 1974; Berglung *et al.*, 1975; Bräutigam *et al.*, 1979; Dijkmans *et al.*, 1981) and others have found it unchanged (Horn and Cottier, 1974; Rosenfeld *et al.*, 1975; Tasker *et al.*, 1975; Dennerberg *et al.*, 1976; Caterson *et al.*, 1978). This discrepancy may be due to the differences in pre-treatment renal function between the patient groups and variations in conditions during treatment.

There have been few reports on the effect of trimethoprim or sulfamethoxazole alone upon measurements of renal function. An increase has been seen in serum creatinine in two individuals during treatment with trimethoprim but this was not seen with sulfamethoxazole (Berglund *et al.*, 1975).

Trimethoprim has been found to be equal or superior to co-trimoxazole or sulfamethoxazole in the treatment of acute, recurrent and chronic urinary tract infections, and it is now widely recommended because of the low incidence of side effects (Brumfitt and Hamilton-Miller, 1982; Barry and Pattishall, 1983).

We felt it important to establish whether or not trimethoprim influences serum creatinine and, if so, to discover the underlying mechanism.

Patients and Methods

We investigated 15 volunteers with no history of either acute or chronic urinary tract infection. All had serum creatinine in the normal range: 50 to 120 μmol/l. They were clinically stable before, during and after the investigation. None was treated with drugs that are known to influence renal function. Two groups were studied. Group A comprised three men and six women (median age 78 years; range 62-92). Group B comprised six men (median age 29 years; range 24-31).

Both groups were treated with trimethoprim 200 mg bd for 14 days. In group B ^{51}Cr-EDTA clearance and 24-h endogenous creatinine clearance were measured before and after therapy.

Blood samples for serum creatinine determi-

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nation were drawn before, during and after treatment and stored at −20°C. The blood samples for each individual were analysed in random order at the end of the investigation. Serum creatinine was measured by the alkaline picrat method of Jaffe on a Technicon Auto Analyzer (SMAC™) (interassay coefficient of variation: 2%). The *in vitro* addition of trimethoprim to serum in a therapeutic concentration (5 mg/l) had no influence on the measurement of serum creatinine.

^{51}Cr-EDTA clearance was measured by the single injection technique as described by Bröchner-Mortensen and Rödbro (1976); 24-h endogenous creatinine clearance was determined in 4-day periods before and at the end of treatment. Blood samples for serum creatinine analysis were drawn in the morning and urine was collected for 24-h periods. The mean value for each 4-day period of endogenous creatinine clearance was calculated. Wilcoxon's test for paired and unpaired differences was used for statistical analyses.

Results

In both groups the serum creatinine values in the days preceding therapy were not significantly different. During the first week of treatment, serum creatinine rose by 34% in group A ($P < 0.01$) and 23% in group B ($P < 0.05$). There was a statistically significant reduction of 10% ($P < 0.02$) in serum creatinine in group A during the second week but in group B it remained constant. One week after treatment, serum creatinine had returned to normal in both groups ($P < 0.02$; $P < 0.05$) (Tables 1 and 2). There was no significant difference between the ^{51}Cr-EDTA clearance before and at the end of the treatment period (Table 3). The 24-h endogenous creatinine clearance at the end of the treatment period was reduced by 22% compared with the pre-treatment value ($P < 0.05$) (Table 3).

Discussion

In the clinical investigation of the influence of a drug in man, it is important to maintain stable conditions before, during and after the investigation. However, this is difficult to achieve in many clinical situations. The effect of co-trimoxazole on renal function has been investigated in many unstable clinical situations and in patients with either normal or impaired renal function, and this may be the main reason for the variation in results (Kalowski *et al.*, 1973; Horn and Cottier, 1974; Berglund *et al.*, 1975; Rosenfeld *et al.*, 1975; Tasker *et al.*, 1975; Dennerberg *et al.*, 1976; Bräutigam *et al.*, 1979; Dijkmans *et al.*, 1981).

Table 1 Group A: Serum Creatinine Before (Day −5), During (Day 0-14) and after (Day 21) Treatment with Trimethoprim 200 mg bd

		Serum creatinine μmol/l				
Patient number	*Day*	*−5*	*0*	*7*	*14*	*21*
1		69	88	95	86	83
2		49	83	138	117	110
3		85	88	104	82	89
4		83	104	120	115	90
5		78	89	150	116	75
6		79	111	128	123	94
7		105	105	147	138	104
8		125	119	141	137	123
9		83	76	134	139	73
Median		83	89	134	117	90
Mean		84.0	96	129	117	93
P	n.s	<0.01	<0.02	<0.02		

We found no significant difference between serum creatinine values measured on different days before and after treatment with trimethoprim, indicating stable conditions. There was a significant, reversible increase in serum creatinine in both groups during treatment. This increase was compatible with previous findings during treatment with co-trimoxazole (Berglund *et al.*, 1975; Bräutigam *et al.* 1979; Dijkmans *et al.*, 1981). Our results confirm the suggestion by Berglund *et al.* (1975) that trimethoprim treatment by itself can increase serum creatinine.

The renal glomerular filtration rate measured by ^{51}Cr-EDTA clearance did not change during treatment. In contrast, we found a 22% reduction in 24-h endogenous creatinine clearance. The same changes have been seen during treatment with co-trimoxazole (Kalowski *et al.*, 1973; Berglund *et al.*, 1975; Shouval *et al.*, 1978; Bräutigam *et al.*, 1979).

The addition of trimethoprim to serum did not affect the creatinine analysis, but we have not investigated the influence of trimethoprim metabolites. However, such an interaction on the creatinine assay would be expected to show the same tendency in serum and urine determinations of creatinine, but we found an increase in serum creatinine and a decrease in creatinine clearance during treatment. Thus our findings cannot be explained by the interference of trimethoprim and its metabolites with the creatinine analysis.

Table 2 Group B: Serum Creatinine before (Day −4-0) During (Day 0-14) and after (Day 21) Treatment with Trimethoprim 200 mg bd

Patient number	Day	*Serum creatinine μmol/l*											
		−4	*−3*	*−2*	*−1*	*0*	*7*	*10*	*11*	*12*	*13*	*14*	*21*
1		88	88	91	91	90	105	118	118	107	110	99	91
2		91	99	91	92	92	108	116	111	127	119	119	98
3		101	100	102	108	100	111	123	112	126	116	116	89
4		83	81	77	73	70	93	103	101	112	95	89	70
5		88	84	81	72	78	103	130	112	97	92	95	85
6		81	78	85	82	84	114	98	98	90	85	91	84
Median		88.0	86.0	88.0	86.5	87	106.5	117.0	111.5	109.5	102.5	97.0	87.0
Mean		88.7	88.3	87.8	86.3	85.7	105.7	114.7	108.7	109.8	102.8	101.5	86.2
P			n.s.	n.s.	n.s.	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	<0.05

Table 3 Group B: 24-hour Endogenous Creatinine Clearance and ^{51}Cr-EDTA Clearance before (I) and after II 14 Days' Treatment with Trimethoprim 200 mg bd

Patient number	*Creatinine clearance ml/min/1.73 m²*		*^{51}Cr-EDTA clearance ml/min/1.73 m²*	
	I	*II*	*I*	*II*
1	97.4	63.2	105	95
2	94.3	84.8	109	107
3	76.4	72.2	78	82
4	132.0	101.2	103	110
5	147.9	92.7	107	85
6	120.2	108.5	82	82
Median	108.8	88.8	104	90
Mean	111.4	87.1	97.3	93.5
P		<0.05		n.s.

Creatinine and 90 to 95% of absorbed trimethoprim are cleared from serum by renal glomerular filtration and renal tubular secretion (Shannon, 1935; Sharpstone, 1969; Patel and Welling, 1980). The findings of an unchanged glomerular filtration rate, decreased 24-h endogenous creatinine clearance and elevated serum creatinine are therefore consistent with inhibition of the tubular secretion of creatinine by trimethoprim. There was no difference between the endogenous creatinine clearance and the ^{51}Cr-EDTA clearance at the end of the treatment period. This indicates that the tubular secretion of creatinine was inhibited to a level where the endogenous creatinine clearance was a measure of the GFR.

The magnitude of the observed change in creatinine clearance during treatment with trimethoprim is great enough to explain the previously reported disturbances in renal function during treatment with co-trimoxazole, but whether sulfamethoxazole also contributes has to be clarified.

The individuals in group A were considerably older than those in group B, but all had normal serum creatinine and the increase in serum creatinine expressed in percentages of pre-treatment value was independent of age.

It is concluded that persons with normal renal function have a reversible increase in serum creatinine during treatment with trimethoprim. These results are consistent with a trimethoprim-induced inhibition of the tubular secretion of creatinine. The increase in serum creatinine was so great that it might be misinterpreted as dehydration or deterioration in renal function. Therefore, changes in serum creatinine during trimethoprim therapy must be evaluated carefully.

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The Authors

J Kastrup, MD, Investigator, Department of Internal Medicine and Endocrinology and Department of Clinical Chemistry

P Petersen, MD, Investigator, Department of Internal Medicine and Endocrinology.

R. Bartram, MD, Investigator, Department of Internal Medicine and Endocrinology

J Molholm Hansen, MD, Consultant Physician in Charge, Department of Internal Medicine and Endocrinology.

Requests for reprints to. J. Kastrup, Department of Clinical Physiology, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 København NV, Denmark.

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Biochemical Studies in Paraplegic Renal Stone Patients.

1. Plasma Biochemistry and Urinary Calcium and Saturation

R. G. BURR and I. NUSEIBEH

Ludwig Guttmann Institute of Spinal Injuries, Stoke Mandeville Hospital, Aylesbury

Summary—Renal stone disease is a common problem in patients with spinal cord injury. The factors responsible are thought to include hypercalciuria and chronic urinary infection. There have, however, been no comparative studies of urinary composition in patients with neuropathic bladder with and without renal stone disease.

Blood, 24-h urine samples and circadian variation of urinary composition were studied in male paraplegic patients with renal stone disease accompanied by urinary infection and in similar patients without stone disease with and without urinary infection.

Two categories of stone patients were recognised, according to whether or not urinary oversaturation with magnesium ammonium phosphate occurred. The urine of all stone patients was oversaturated with calcium phosphate for part of each day.

Urinary calcium was elevated in 16% and plasma urate in 30% of the paraplegics studied.

Renal calculi in patients with spinal cord injury are usually associated with chronic infection of the urinary tract and invariably contain magnesium ammonium phosphate (MAP) (Burr, 1981). Frequent oversaturation of urine with MAP is therefore expected in such patients.

Elevated urinary calcium and plasma urate are commonly observed during the first few months following injury to the spinal cord and both are risk factors for certain types of urinary stone (Minaire *et al.*, 1981). Hypercalciuria in particular has been implicated in stone formation in paraplegia (Freeman, 1949).

There have been no comparative studies of plasma calcium and urate or of urinary calcium and saturation levels in patients with neuropathic bladder with and without stone disease.

Patients and Methods

The renal stone-formers were male patients with spinal cord lesions and chronic urinary tract infection (Table 1). Their calculi were of the calcareous, radio-opaque type; patients with matrix calculi were excluded. Quantitative chemical analysis of the stones available from 23 of the patients showed them to consist of calcium phosphate and MAP;

Table 1 Male Patients with Spinal Cord Lesions

	Non-stone	*Renal stone-formers*
Age (years)	16-77 (mean 40.3)	21-73 (mean 40.4)
Duration of cord lesion (years)	0.6-46 (mean 11.2)	0.5-35 (mean 14.4)
Number of patients studied by		
blood sampling†	27	27
24-h urine collection†	43 (30)*	32 (32)*
circadian variation†	26 (16)*	26 (26)*

* The figures in parenthesis are the numbers of patients with urinary infection.

† The ages of the patients in these groups, and the durations and levels of their cord lesions, did not differ significantly.

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Table 2 Serum Values in Stone and Non-stone-forming Paraplegics and in Healthy Control Subjects

	Non-stone *n* = 27	*Stone* *n* = 27	*Control* *n* = 20
	mean sd	mean sd	mean sd
Total calcium	2.26 ± 0.11	2.32 ± 0.10	2.30 ± 0.12
Ionised calcium	1.17 ± 0.04	1.18 ± 0.04	1.15 ± 0.05
Inorganic phosphate	1.20 ± 0.17	1.12 ± 0.15	1.24 ± 0.14
Albumin	38.7 ± 3.9	40.7 ± 5.3	44.1 ± 2.45
Total protein	67.0 ± 6.9	69.7 ± 5.2	67.2 ± 3.52
Urate	370 ± 50	390 ± 80	366 ± 78
Chloride	104.2 ± 2.7	103.3 ± 3.0	
Bicarbonate	28.9 ± 1.75	28.1 ± 1.9	

All values are in mmol/l.

urate was not detected (enzymically) and the maximum concentration of calcium oxalate (oxalate oxidase method, Sigma, Poole) was 10 mg/g dried calculus. Test for urinary cystine was negative. In six of the 32 stone-formers renal stones first appeared within 1 year of onset of the cord lesion; in two others the possibility that a stone was present previously could not be excluded. In the other 24 patients the calculi first appeared more than 1 year after the onset of the cord lesion.

The patients with no history of calculosis in any part of the urinary tract (Table 1) were male patients with spinal cord injury who had been admitted for minor surgery, for treatment of a pressure sore, or for rehabilitation.

Venous blood samples were obtained with a minimum of venous stasis, with the patients fasting and having been in the supine position for at least 45 min. No patient was in renal failure or receiving steroid or diuretic therapy. Serum calcium, inorganic phosphate, albumin, total protein and urate were determined by Technicon SMA II, plasma chloride and bicarbonate by Technicon 660. Serum ionised calcium was calculated by the method of Pottgen and Davis (1976).

Blood samples were also obtained under the same conditions from 20 apparently healthy members of the hospital staff. Their mean age was 34.4 years. Calcium, inorganic phosphate, albumin, total protein and urate were determined and ionised calcium calculated as before.

One to 16 (mean 5.7) 24-h collections of urine per patient were obtained from 75 patients and the circadian variation of urinary composition studied by collecting 14 to 18 separate urine samples during a 48-h period from 52 patients (Table 1). Preservation and analysis of specimens were carried out and relative saturation (RS) of urine samples with brushite, octacalcium phosphate (OCP) and MAP calculated as described by Burr and Nuseibeh (1983).

Urine was cultured routinely in the Bacteriology Department of the hospital by inoculation of CLED media followed by incubation overnight at 37°C.

Results

Plasma composition did not differ between paraplegics with stones, paraplegics without stones or control subjects (Table 2). All of the serum calcium, phosphate and bicarbonate results were within normal limits. Ten stone-formers, six non-stone patients and three control subjects had plasma urate levels over 420 µmol/l.

Table 3 gives the results of analysing 24-h urine samples. Ammonium excretion, pH and RS values were significantly higher in the stone patients than in the non-stone patients whether urinary infection was present in the latter or not. There was no significant difference in calcium excretion between stone and non-stone patients. Five of 32 stone patients and 8 of 43 non-stone patients excreted more than 7.5 mmol calcium/24 h. There was no difference in the urinary excretion of any substance measured between patients who started to form their calculi before or after the end of the first year following onset of the cord lesion.

The 24-h samples were oversaturated with brushite and/or OCP in 13 of 25 infected non-stone patients and in 25 of 27 stone-formers. None of 33 non-stone and 3 of 27 stone-formers' urine samples were oversaturated with MAP.

In the circadian study, calcium phosphate oversaturation was observed for part of the day in 8 of 10 patients without urinary infection, in 13 of 16

Table 3 Results of Analyses of 24-h Urine Samples. Means ± Standard Deviations are Given.

	Non-stone	*Non-stone*		*Stone-formers*
Urine culture	*No growth*	*Infected*		*Infected*
pH	6.34 ± 0.195	6.53 ± 0.438	***	7.10 ± 0.561
Ammonium (mmol/24 h)	29.5 ± 5.85	32.7 ± 14.93	***	57.5 ± 36.05
Brushite relative saturation	+0.21 ± 0.216	+0.05 ± 0.498	*	+0.24 ± 0.290
OCP relative saturation	−0.02 ± 0.287	−0.24 ± 0.649	**	+0.17 ± 0.418
MAP relative saturation	−4.3 ± 0.94	−4.7 ± 2.00	**	−2.7 ± 2.34
Sodium (mmol/24 h)	139 ± 43.7	142 ± 50.3		153 ± 41.0
Potassium (mmol/24 h)	67.0 ± 17.9	58.6 ± 22.0		60.4 ± 12.5
Calcium (mmol/24 h)	†4.65 ± 1.53	4.75 ± 2.87		5.39 ± 2.19
Magnesium (mmol/24 h)	4.55 ± 1.38	3.99 ± 1.67		3.85 ± 0.93
Inorganic phosphate (mmol/24 h)	26.9 ± 6.91	21.0 ± 6.85		21.6 ± 5.45
Creatinine (mmol/24 h)	9.9 ± 1.98	8.5 ± 2.64		8.4 ± 2.02
Volume (litre/24 h)	2.76 ± 0.87	3.16 ± 1.38		3.59 ± 1.36

† Result on one patient with spinal cord lesion < 1 year excluded.

* Difference between stone-formers and infected non-stone patients significant: $0.05 > P > 0.02$.

** Difference between stone-formers and infected non-stone patients significant: $0.01 > P > 0.001$.

*** Difference between stone-formers and infected non-stone patients significant: $P < 0.001$.

OCP: octacalcium phosphate; MAP: magnesium ammonium phosphate.

infected non-stone patients and in all 26 stone patients. MAP oversaturation was seen in no patient without urinary infection, in 3 of 16 infected non-stone patients and in 10 of the 26 stone patients.

There was a well marked circadian variation of urinary pH in the 10 patients who were not infected (Fig. 1). The pH was lowest between 01.00 and 05.00 h and highest between 09.00 and 17.00 h. Ammonium concentration was inversely related to pH and the RS values paralleled the changes in pH.

Eight patients had exceptionally alkaline urine (pH > 8 for part of the day) and a positive correlation between pH and ammonium concentration. A physiological increase in urinary pH is associated with a decrease in renal ammonia production; infection by urea-splitting organisms leads to increases in both pH and ammonium. These patients were therefore assumed to have overt urease-positive infection. The circadian variations of pH, $\mathrm{RS}_{\mathrm{brushite}}$ and $\mathrm{RS}_{\mathrm{OCP}}$ were variable and inconsistent, but there were large circadian changes in ammonium concentration and in $\mathrm{RS}_{\mathrm{MAP}}$, high values occurring frequently, but not invariably, at night when the urine was concentrated. In most of these patients there was a positive correlation between $\mathrm{RS}_{\mathrm{MAP}}$ and creatinine concentration. The greatest difference in urinary composition between the patients with no urinary infection and those with urease-positive infection was found in the samples collected from 01.00 to 05.00 h.

Following Robertson and Peacock (1982), ammonium concentration was plotted against pH for all of the urine samples collected from the patients with no infection and those with overt urease-positive infection as defined above (Fig. 2). Based on the distribution of points, the quantity

$$(\text{ammonium concentration}) + 22.\text{pH}$$

where ammonium concentration was expressed in mmol/l was calculated. The regression of $\mathrm{RS}_{\mathrm{MAP}}$ on $([\mathrm{NH}_4^+] + 22.\mathrm{pH})^{-2}$ for 698 urine samples gave a correlation coefficient, r, of −0.887. The use of either $\mathrm{RS}_{\mathrm{MAP}}$ or $([\mathrm{NH}_4^+] + 22.\mathrm{pH})$ gave a better discrimination between the two groups than either pH or NH_4^+ alone (Fig. 3).

The values for all patients are shown in Figure 4. Forty-seven per cent of stone-formers' values lay within the range of the patients without infection.

There were positive correlations between pH and both $\mathrm{RS}_{\mathrm{brushite}}$ and $\mathrm{RS}_{\mathrm{OCP}}$. The pH corresponding to the commencement of oversaturation varied in different patients between pH 6 and 8. In some patients undersaturation was not present unless the pH was 5.5 or less. By contrast, MAP oversaturation was observed only at pH 6.7 or above.

Discussion

Sixteen per cent of patients (stone- and non-stone-formers) had hypercalciuria (urinary calcium over 7.5 mmol/24 h) and 30% had hyperuricaemia (plasma urate above 420 µmol/l). Since, however, there were no significant differences between stone

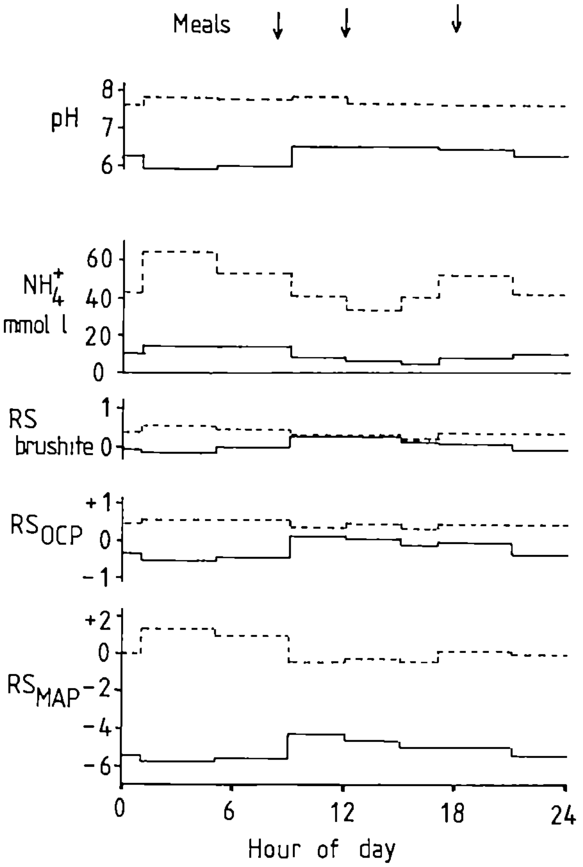

Fig. 1 Circadian variation of urinary composition in 10 patients with no urinary infection and in 8 with infected alkaline urine (pH > 8 for part of day). Solid line: no infection; broken line: infected

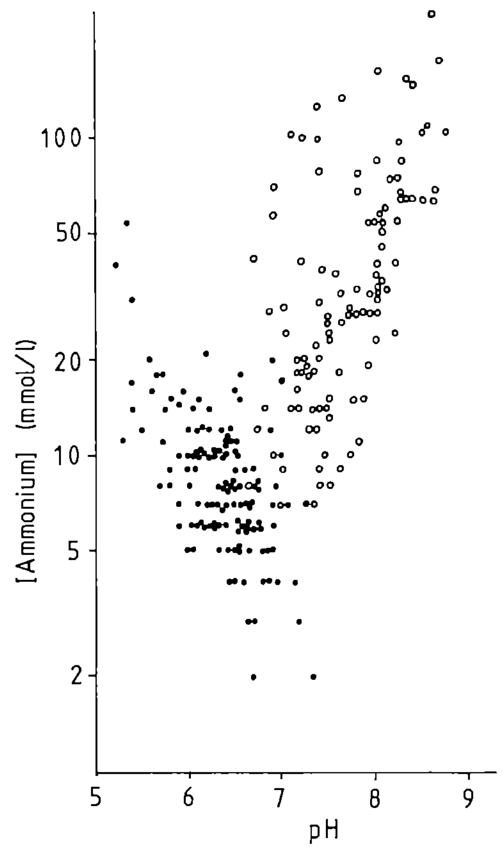

Fig. 2 Urinary pH and ammonium concentration in 10 patients with no urinary infection and in 8 with infected alkaline urine: 14-18 samples collected through 48 h. Closed circles: no infection; open circles: infected.

and non-stone patients it cannot be said whether these abnormalities relate to an increased risk of calculus formation in paraplegic patients.

The circadian variation of urinary composition in the patients without urinary infection followed the well recognised pattern of an "alkaline tide" following meals. The patients with presumed overt urea-splitting infection had elevated pH and ammonium, with exaggerated ammonium production at times when the rate of urine flow was reduced. The remaining patients with urinary infection with or without stone disease had either no increase or a slight increase in pH or ammonium concentration (Fig. 4), with the exception of three patients without stones who had a marked increase; one later developed a matrix calculus.

The great variability in saturation values observed at different times in the same patient explains why oversaturation with MAP was observed in only 11% of stone patients based on 24-h urine samples but in 38% based on circadian samples. The value of analysing a single random specimen of urine from a patient is therefore limited. Analysis of a series of small samples collected throughout 48 h enabled the peak saturation to be recognised.

The function ([NH_4^+] + 22.pH) required fewer analyses and was simpler to calculate than RSMAP, correlated well with the latter and yielded a good discrimination between patients with and without urease-positive infection (Fig. 3). A value in the range 180 to 200 corresponded to saturation with MAP; most values in patients without urinary infection lay below 165.

Oversaturation with MAP observed in 38% of stone-formers suggested the presence of urease-positive organisms and provided a sufficient explanation for the presence of stone disease. Failure to observe MAP oversaturation in the other stone patients may indicate that their calculi were not infection-induced (Griffith, 1982). It is possible,

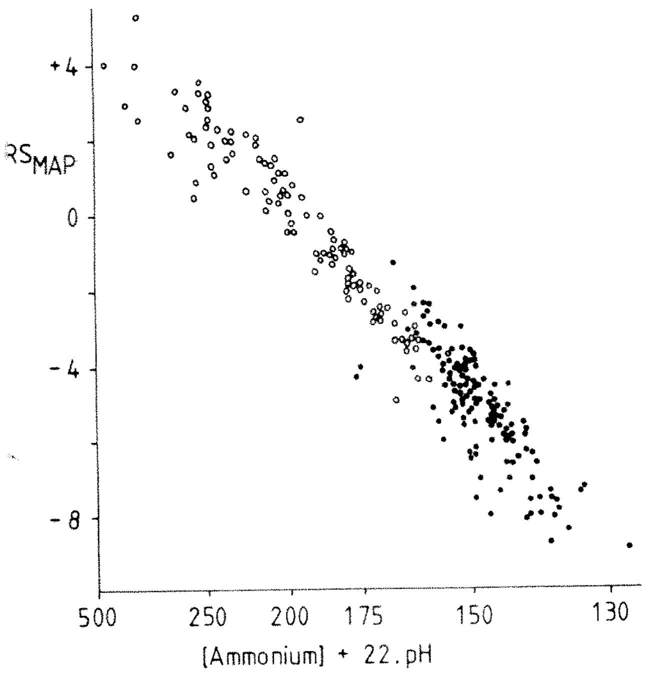

Fig. 3 Urinary MAP saturation and ([NH$_4^+$]+22.pH) in 10 patients with no urinary infection and in 8 with infected alkaline urine: 14-18 samples collected through 48 h. Closed circles: no infection; open circles: infected.

however, that MAP oversaturation was localised at the stone surface, where the organisms responsible were present in greater numbers than elsewhere in the urinary tract. Alternatively, MAP oversaturation may be a spasmodic phenomenon, occurring only occasionally as a result of periodic exacerbations of urea-splitting infection. A specific bacteriological or biochemical test for urease-positive organisms was not carried out.

In six patients renal calculi had appeared within 1 year of onset of the spinal cord lesion. It is possible that in these patients stone formation had been "triggered" (Vermeulen *et al.*, 1967) by hypercalciuria, perhaps together with an episode of dehydration or urease-positive infection. The patients with calculi that first appeared at a later stage of paraplegia may also have experienced a short-lived "trigger" phase. Once a stone had begun to form, its growth would have been ensured by repeated episodes of oversaturation with calcium phosphate, which was observed in all of the stone patients. Alternating episodes of under- and over-saturation will result in growth of an existing stone, since surface adsorption of macromolecules will hinder dissolution at times when the urine is undersaturated. In addition, amorphous calcium phosphate first precipitated is known to "age" via OCP to the less soluble hydroxyapatite (Wuthier and Eanes, 1975). The importance of avoiding periods of underhydration, particularly at nighttime, is made clear by this study.

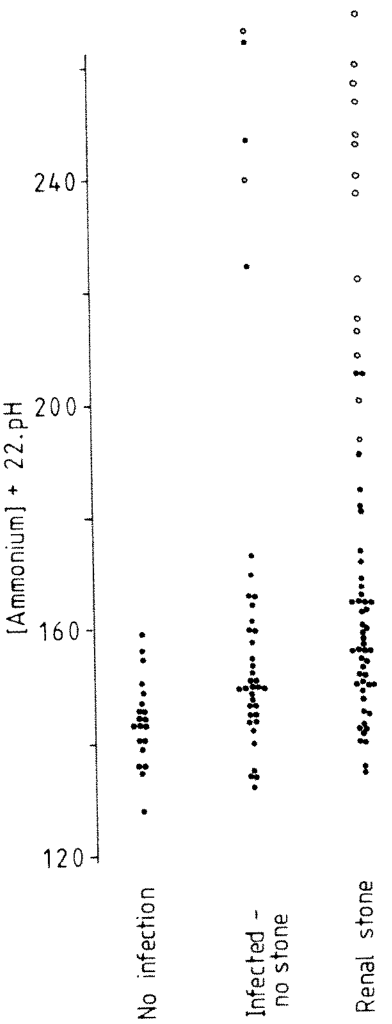

Fig. 4 Results on urine samples collected from 01.00 to 05.00 h from 10 patients with no urinary infection, 16 patients with urinary infection without stones and from 26 infected renal stone-formers (2 specimens per patient). The values for patients with highly alkaline urine are shown by open circles.

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The Authors

R. G. Burr, PhD, FRSC, Biochemist.
I Nuseibeh, FRCS, Consultant in Spinal Injuries

Requests for reprints to: R. G. Burr, Ludwig Guttmann Institute of Spinal Injuries, Stoke Mandeville Hospital, Aylesbury HP21 8AL.

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Biochemical Studies in Paraplegic Renal Stone Patients

2. Urinary Excretion of Citrate, Inorganic Pyrophosphate, Silicate and Urate

R. G. BURR, I. NUSEIBEH and C. D. ABIAKA

Ludwig Guttman Institute of Spinal Injuries, Stoke Mandeville Hospital, Aylesbury

Summary—The urinary excretions of citrate, inorganic orthophosphate and pyrophosphate, silicate and urate were measured in 17 paraplegic patients with renal calculous disease associated with urinary infection, in 16 paraplegics with no history of urinary calculus and in 14 healthy control subjects.

The paraplegics excreted less citrate, orthophosphate and pyrophosphate than the control subjects. The stone-formers excreted more urate than the paraplegics without stone disease, but less than the control subjects. There were significant positive correlations between urinary orthophosphate and pyrophosphate and between urinary silicate and 24-h urine volume.

The possible roles of increased urate and diminished excretion of citrate and inorganic pyrophosphate in the aetiology of renal calculosis in paraplegic patients deserve further investigation.

Renal calculi produced by paraplegic patients are usually infective in origin (Burr, 1981). Changes in the composition of the urine are those associated with infection by urea-splitting organisms, but these findings provide only a partial explanation for the growth of calculi in paraplegics (Burr and Nuseibeh, 1984).

There have been conflicting reports on the presence or absence of urate in calculi from paraplegics (Burr, 1978; Minaire *et al.*, 1981) and silicate in infected calculi (Zinsser *et al.*, 1968; Burr, 1976). Urinary citrate is frequently found to be low in patients with renal stones both with (Wikstrom *et al.*, 1981) and without (Rudman *et al.*, 1982) renal tubular acidosis. Inorganic pyrophosphate (PP_i) excretion is also low in some patients with renal calculus (Fleisch, 1978). The roles of citrate and PP_i in urolithiasis following paraplegia have not been investigated.

In other types of calcium renal stone disease, citrate and PP_i are inhibitors of crystal formation in urine, while urate and possibly polymeric silica are promoters (Thomas 1969; Fleisch, 1978). We have therefore measured urinary citrate, PP_i, silicate and urate in stone- and non-stone-forming paraplegics as well as in control subjects.

Patients and Methods

Table 1 gives data relating to the subjects studied, all of whom were male: paraplegics with renal stones and chronic urinary infection; paraplegics with no history of urinary stone, who were studied while in hospital on account of pressure sores or for minor surgery; and non-paraplegic volunteers in apparently good health.

Twenty-four-hour urine samples were obtained with the receiver kept in ice. Citrate was determined on the day of completion (Welshman and McCambridge, 1973). An aliquot was rendered alkaline (1 drop 40% NaOH per 10 ml urine) and urate determined within 5 days by a uricase method (Urica Color, Boehringer Corporation, Lewes). Another aliquot was acidified to pH 2 (conc HCl)

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Table 1 Subjects Studied. All were Male

	Paraplegics		*Non-paraplegics*
	Renal stone	*Non-stone*	
Number	17	16	14
Age (years)	21-62 (mean 44.0)	21-70 (mean 40.9)	22-76 (mean 42.9)
Duration of paraplegia (years)	0.9-27 (mean 14.0)	1.1-38 (mean 13.5)	
Duration of stone disease (years)	0.1-13 (mean 4.2)		
Spinal cord lesion	8 cervical 9 thoracic	7 cervical 9 thoracic	
Number with positive urine culture	17	9	0

and stored at 4°C for determination of inorganic phosphate and creatinine by automated spectrophotometry. A further aliquot was stored at 4°C and analysed within 5 days for silicate. Finally, an aliquot was stored at −20°C and analysed within 5 days for PP_i.

Silicate was determined by the method of Paul (1960) modified by the use of NaOCl to remove ascorbate present in the samples and by the use of imidazole to facilitate buffering to pH 7.0 in the phosphate precipitation step.

After separation on a column (Russell and Hodgkinson, 1966) PP_i was determined as follows. To 1 ml eluate (in HCl, 1 mol/l) add 500 µl H_2SO_4 (1.8 mol/l), 500 µl ammonium molybdate (30 g/l) and 30 µl hydrazine hydrate (1.4 mol/l). After 35 min read absorbance at 710 nm. This procedure gave a calibration curve that was linear in the range 0 to 100 µmol/l, recovery 87 to 107.5% (mean 94.3). coefficient of variation 3.8% and sensitivity 0.5 to 1 µmol/l.

Creatinine clearance was obtained for the patients only by collection of a separate 24-h urine sample and venous blood sampled during the same period.

Results

Table 2 summarises the results. The patients excreted less citrate, creatinine, orthophosphate, PP_i and urate than the control subjects. Twenty-four-hour urine volumes were higher, and the concentrations of citrate and PP_i lower, in the stone patients than in the non-stone patients. Urate excretion in the stone-formers was higher than in the non-stone patients but lower than in the control subjects. The numbers of subjects excreting more than 3 mmol urate/24 h were: patients without stones, 0; stone-formers, 4; control subjects, 9. One stone patient and 2 control subjects excreted more than 4 mmol urate/24 h.

There was a positive correlation between the excretions of orthophosphate and PP_i ($r = 0.537$).

Silicate excretion showed a positive correlation with 24-h urine volume; for the patients $r = 0.775$ and for the control subjects $r = 0.685$. From one

Table 2 Results of the Urine Analyses

	Paraplegics		*Non-paraplegics*
	Renal stone	*Non-stone*	
	m ± *s.d.*	*m* ± *s.d.*	*m* ± *s.d.*
Citrate (mmol/24 h)	1.65 ± 1.09[1]	1.59 ± 0.77[2]	2.67 ± 1.79
Creatinine (mmol/24 h)	7.80 ± 2.11[1]	9.15 ± 2.20[1]	14.6 ± 4.04
Creatinine clearance (ml/min)	47.6 ± 33.3[4]	65.7 ± 42.4	
Inorganic orthophosphate (mmol/24 h)	18.1 ± 6.57[1]	20.7 ± 6.70[1]	37.7 ± 10.2
Inorganic pyrophosphate (µmol/24 h)	11.2 ± 10.4[1]	18.4 ± 13.3[2]	37.3 ± 20.7
Silicate (mmol/24 h)	1.35 ± 0.38	1.06 ± 0.43	1.20 ± 0.583
Urate (mmol/24 h)	2.45 ± 0.80[2,5]	1.97 ± 0.39[1]	3.20 ± 0.80
Volume (litre/24 h)	3.63 ± 1.11[2,3]	2.16 ± 0.84	2.14 ± 1.29

1: Significantly different from the non-paraplegics ($P < 0.001$).
2: Significantly different from the non-paraplegics ($0.01 > P > 0.001$)
3: Significantly different from the non-stone paraplegics ($P < 0.001$).
4. Significantly different from the non-stone paraplegics ($0.01 > P > 0.001$).
5 Significantly different from the non-stone paraplegics ($0.05 > P > 0.02$)

healthy male ten 24-h urine samples were obtained with volumes in the range 0.8 to 4.8 litres; for these $r = 0.812$. When the effect of urine volume was taken into account there were no differences in silicate excretion between stone-formers, patients without stone disease and control subjects.

No differences were observed between patients with and without infection of the urinary tract and there were no significant correlations between creatinine excretion or clearance and any of the other substances determined.

Discussion

The low urinary citrate excretion observed in the paraplegics without stone disease was not expected. Citrate excretion is reduced in patients with acidosis, with potassium or magnesium depletion, during therapy with certain drugs and when the dietary intake of citrate is low (Rudman, 1980). Plasma bicarbonate was within normal limits in the patients in this study, and no patient was receiving diuretic or uricosuric therapy. There is no evidence of magnesium depletion during the acute phase of paraplegia (Broughton and Burr, 1972) and urinary potassium and magnesium excretion in chronic paraplegics is normal (Burr and Nuseibeh, 1985). Urinary citrate did not correlate with creatinine clearance.

Certain micro-organisms are capable of utilising citrate (Cowan, 1974) and these include bacteria frequently isolated from the urine of paraplegic patients. We have observed that citrate is stable in sterile urine but lost rapidly from most infected urine unless the sample is acidified or refrigerated. We have also found that, in patients without urinary infection and with normal plasma bicarbonate, urinary citrate tends to be lower in bedfast than in mobile patients, and can be greatly increased in some by supplementing the diet with citrous juice. We therefore attribute our findings to the effects of posture, infection and low dietary citrate and continue to search for other factors involved.

In health the excretion of inorganic phosphate varies widely, depending on the diet. A relationship between the excretions of PP_i and orthophosphate is well recognised (Russell and Hodgkinson, 1966). We therefore attribute low urinary PP_i to low urinary orthophosphate due to a low dietary intake of phosphorus. PP_i is destroyed by certain bacteria (Timmermann *et al.*, 1969) but there was no evidence of this in the present work.

Thomas (1969) reported that polymeric silica was a promoter of mineralisation and a blocker of some urinary crystallisation inhibitors. Monomeric silica was without effect but 20 to 30% of silica in urine was in the polymeric form. Silicate calculi have resulted from high dosage magnesium trisilicate therapy (Herman and Goldberg, 1960; Lagergren, 1962; Lipworth *et al.*, 1964; Nutrition Reviews, 1982) and in one study infected calculi contained up to 6% silica (Zinsser *et al.*, 1968).

Urinary silicate has been infrequently measured. The method we used was specific and rapid. We found no evidence to link urinary silicate with stone disease in paraplegic patients. Silicate excretion depended on the volume of urine produced. We could not detect polymeric silica in human urine. The monomer is the stable form of silica in solution when the concentration is less than 1.8 mmol/l (Alexander *et al.*, 1954). The highest silica concentration in our urine samples was 1.5 mmol/l.

Urate excretion was higher in the stone-formers than in the patients without stone disease. The significance of this observation is, however, made doubtful by the very high values of the control group and the fact that, owing to the higher 24-h volumes of the stone-formers, the concentration of urate did not differ between the two groups of patients. There was no correlation between urinary and plasma urate. We have not so far detected urate in any calculus produced by a paraplegic (in 160 stones analysed) although others have. Urate excretion is elevated during the first 30 weeks following the onset of a spinal cord lesion as a component of the well-recognised negative nitrogen balance at this time (Minaire *et al.*, 1981).

Citrate and PP_i inhibit the formation and growth of crystals of calcium phosphate (Fleisch, 1978). Elevated urinary urate is a risk factor in certain types of calcium stone disease (Robertson and Peacock, 1982). Whether the low urinary citrate and PP_i in the paraplegics in this study, and the raised urinary urate in the stone-formers, are related in any way to the high incidence of renal calculi in paraplegia requires further study.

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The Authors

R. G. Burr, PhD, FRCS, Biochemist.
I Nuseibeh, FRCS, Consultant in Spinal Injuries
C. D Abiaka, FIMLS, Medical Laboratory Scientific Officer

Requests for reprints to: R G. Burr, Ludwig Guttmann Institute of Spinal Injuries, Stoke Mandeville Hospital, Aylesbury HP21 8AL.

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Management of the Posterior Peritoneum after Transperitoneal Renal Surgery

R. CIEŚLIK and L. CERKOWNIK

Department of Surgery, District Hospital, Przemysl, Poland

Summary—Between 1977 and 1982, 15 patients underwent renal operations carried out transperitoneally and in none was the posterior peritoneum reconstituted. There were no significant complications.

The classical lumbar approach to the kidney may not always be the best route of access for operations, particularly when inflammatory or neoplastic conditions obscure the renal pedicle or obliterate the anatomical margins of the kidney. One hundred years ago Kocher realised this but, apart from Berg, it was a long time before there was real interest in a transperitoneal approach to the kidney because of frequent complications. Then, in the 1960s, Poutasse (1961) and Quist (1963) recommended an anterior route to the upper urinary tract. In the Polish literature, Wesolowski (1976), Stolarczyk and Otreba (1966) and Stolarczyk *et al.* (1980) strongly recommended this approach for nephrectomies for tumour or for trauma, and also for operations on the renal pelvis with simultaneous cholecystectomy. In recent years, it was suggested that re-suture of the posterior peritoneum was not necessary after removal of some abdominal organs (Hubbard *et al.*, 1967; Kortas and Zalewski, 1975; Cieślik, 1977), and experimental and clinical observations confirmed that unsutured posterior peritoneal defects healed by regeneration without adhesions and avoided many of the post-operative complications noted after primary peritoneal suturing (Cieślik, 1979). Consequently, it became the practice in our department to leave the posterior peritoneum unsutured after transperitoneal operations on the kidney and the results of this policy are presented in this report.

Patients and Methods

Fifteen patients (12 male, 3 female; age range 16–74 years) underwent renal surgery between 1977 and 1982 using a transperitoneal approach. The operations were carried out with the patient lying supine and some lateral elevation on the side of the procedure. Laparotomy was carried out through an upper transrectal incision with medial mobilisation of upper abdominal structures to expose the lateral paracolic peritoneum. The peritoneum was incised alongside the outer margin of either the ascending or descending colon, which was mobilised medially to expose renal pedicles so that the major vessels could be ligated individually under direct vision if nephrectomy was necessary. When tumour was present, the operations proceeded according to the method described by Stolarczyk *et al.* (1980). The posterior peritoneal incision was not sutured and the renal bed was drained after nephrectomy for pyonephrosis or tumour, but not after removal of traumatised kidneys.

Results

Details of the patients are shown in the Table. Two patients died, one from peritonitis following gunshot injuries to the colon (RM) and the other from acute cardiac failure (MS), but otherwise the remaining 13 patients had a smooth post-operative course without wound infection or ileus.

Discussion

With the increase in injuries resulting from road

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Table Diagnosis, Treatment and Results in 15 Patients

Name	*Sex*	Age (*years*)	*Disease*	*Treatment*
B F	F	46	Right pyonephrosis	Nephrectomy
D J	M	48	Carcinoma of right kidney	Nephrectomy
S S	M	16	Post-traumatic rupture of left kidney	Suture
K J.	M	20	Post-traumatic rupture of right kidney	Nephrectomy
R.M.	M	35	Gun-shot wound of abdomen	Nephrectomy, cholecystectomy of small and large intestine
G.M.	M	32	Post-traumatic rupture of kidney and spleen	Splenectomy, suture of kidney
M Z.	M	61	Rupture of spleen, left perinephric haematoma	Splenectomy, repair of kidney
J.T.	F	41	Stab wounds of abdomen	Splenectomy, repair of ureter
C.S.	M	66	Right pyonephrosis	Nephrectomy
K T	M	56	Right pyonephrosis	Nephrectomy
D S	M	30	Right pyonephrosis	Nephrectomy
M S.	M	74	Left pyonephrosis	Nephrectomy
W.Z.	M	28	Rupture of spleen and kidney	Splenectomy, suture of kidney
J D	M	34	Rupture of liver, contusion of kidney	Suture of liver, repair kidney
J G	F	65	Left pyonephrosis	Nephrectomy

traffic accidents, exploration of injured kidneys during laparotomy will inevitably be more frequent. Exploration is usually carried out transperitoneally and this is the route of choice for many elective renal operations by urologists. Delebiński (1980) suggested that this approach may have a lower per-operative mortality than operations carried out through the flank. Poutasse (1961) and Quist (1963) both recommended that incisions made in the parietal peritoneum to gain access to the kidney and upper ureter should be left unsutured at the end of the operation and our own experimental and clinical experience (Cieślik, 1977, 1979) confirms earlier views of other writers (Hubbard *et al.*, 1967; Kortas and Zalewski, 1975) that this is a safe policy. In fact, re-suturing of the parietal peritoneum may cause post-operative complications. Experimental studies in animals have shown that unsutured peritoneal defects heal by regeneration with new peritoneal tissue, whereas suturing results in strong adhesions, sometimes with associated abscesses and granulomatous development in the neighbourhood of the sutures (Cerkownik, unpublished data).

Post-operative drainage of the renal bed is necessary after transperitoneal operations for carcinoma of the kidney, pyonephrosis or gunshot wounds (Poutasse, 1961; Wesolowski, 1976), but it is not necessary after operations for renal trauma because it is known that non-infected haematomas can be absorbed quickly without adhesion formation.

The number of patients in this study is small but their smooth post-operative course leads us to recommend that after transperitoneal renal operations it is safe to leave the posterior abdominal peritoneal tissue unsutured and open.

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The Authors

R Cieślik, MD, Consultant Surgeon.
L. Cerkownik, MD, Assistant.

Requests for reprints to· R Cieślik, Department of Surgery, District Hospital, ul Rogozińskiego 30, 37-700 Przemysl, Poland

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Ureteroscopy.
An Alternative View

D. A. TOLLEY and L. L. BEYNON

Department of Urology, Royal Infirmary, Edinburgh

Summary—Forty-six ureteroscopies were carried out over a 12-month period. A simple technique is described. The desired level was reached in 72% of cases and the pre-operative objective achieved in 60% of cases overall. Fifty per cent of all ureteric stones were safely retrieved by ureteroscopy. The instrument was used to establish a diagnosis of upper urinary tract abnormality in 16 of 23 cases. The overall complication rate was low, most problems relating to short-lived ureteric colic (23%) which was seen mainly after stone manipulation.

Transurethral ureteroscopy is a safe procedure with a number of diagnostic and therapeutic possibilities.

The arrival of instruments which permit visual inspection of the ureter has increased the role of endourology in the management of patients with upper urinary tract disorders. Although it has been possible to examine the ureter with a flexible instrument since the late 1960s, endoscopic examination of the ureter with a rigid instrument is a relatively new technique pioneered by Pérez-Castro and Martinez-Piñeiro (1982).

This report describes our early experience with the Storz rigid ureteroscope in the diagnosis of upper urinary tract disorders and the extraction of ureteric stones.

Patients and Methods

Ureteroscopy was carried out on 46 occasions in a 12-month period to June 1984. Forty-two patients were included in the series (23 male, 19 female; age 22-78 years). The procedure was for diagnosis in 23 patients, the placement of catheters for the relief of ureteric obstruction in 3 and for stone extraction in 16.

The Storz ureterorenoscope was developed by Pérez-Castro and Martinez-Piñeiro (1982) and is an extended paediatric 11 F cystoscope measuring 50 cm in length. It is used with a 0° forward viewing telescope for inspection of the ureter and upper calices or with an oblique (70°) lens which allows inspection of the renal pelvis and lower calices.

All procedures were carried out under general anaesthesia on a Siemens urological table which permits simultaneous X-ray screening of the ureter whenever necessary.

A preliminary urethrocystoscopy was carried out, at which time the ureteric orifice was identified. A 4 F balloon catheter was introduced into the ureteric orifice and the balloon distended with air by the surgeon, who watched the ureteric orifice and controlled the degree of distension. The balloon was inflated for a minimum of 60 s and the ureteric orifice dilated to approximately 14 F. After dilatation the orifice appeared wide and gaping.

A ureteric catheter was then passed up the ureter, the cystoscope withdrawn and the ureteroscope introduced over the catheter to the site of the ureteric orifice. The instrument was then carefully advanced over the ureteric catheter; if necessary, further distension of the ureter with saline or contrast medium can take place through the catheter. Difficulty may arise in negotiation of the lower third of the ureter and the middle third as it passes over the pelvic brim. Once the ureteric abnormality was seen, the ureteric catheter was withdrawn and a cytology brush, flexible biopsy forceps or Pfister-Schwartz basket introduced through the 4 F instrument channel. Most patients were discharged

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from hospital the same day or within 48 h post-operatively.

Results

Twenty attempts at stone extraction were carried out (Table 1). Provided that the level at which the stone was situated could be reached, successful extraction occurred in 66% of cases. Only two stones were extracted by ureterolithotomy, one stone migrated outside the ureter and the remaining stones all passed spontaneously.

Ureteroscopic diagnosis was attempted on 26 occasions for a variety of reasons, mainly loin pain, haematuria and the elucidation of filling defects seen on intravenous urography. In 70% of cases the level was reached and a diagnosis made in 65% overall.

The ureteroscope was also used to pass ureteric catheters under vision to relieve ureteric obstruction in three cases where attempts at retrograde or antegrade ureteric catheterisation under X-ray control had failed. In all cases it was possible to relieve the obstruction by this method.

Intravenous urograms were carried out on 35 of 42 patients between 3 and 4 months after ureteroscopy. There was no evidence of ureterovesical junction obstruction but in two cases there was evidence of ureteric obstruction. One patient had had previous ureteric surgery and had a stricture pre-operatively and one patient had a difficult ureterolithotomy followed by ureteric leakage.

Discussion

The therapeutic capabilities of this instrument are at present limited, although an operating uretero-resectoscope is shortly to be introduced. With the present instrument, activity is limited to placement of ureteric catheters or stone extraction. The diagnosis of ureteric lesions places great reliance on visual assessment, since we have found that the instruments presently used to obtain cytological specimens and biopsies are unsatisfactory. However, the development of the ureteroresectoscope will make it easier to obtain specimens for histological examination.

The major role of the present instrument would therefore appear to be for stone extraction. We had difficulty in negotiating the ureter at the level of the pelvic brim and we believe that the use of the instrument above this level in obese men is contraindicated since it is virtually impossible to pass the instrument any higher without causing mucosal damage.

The initial difficulties of entering the ureteric orifice and negotiating the lower third of the ureter reported by Ford *et al.* (1983) can, we believe, be overcome by adequate dilatation of the ureteric orifice. The use of the ureteric catheter to "show the way" was invaluable in our early experience. The catheter also appears to straighten out bends in the upper ureter. Other authors have advocated the use of metal bougies or teflon dilators to dilate the ureteric orifice but we prefer to use a Fogarty distensible balloon catheter since it permits more effective dilatation.

Clearly one should not attempt to extract stones more than 1 cm in diameter from the ureter, but the development of ultrasonic and electrohydraulic methods of stone extraction may facilitate larger stone extraction. Five of six attempts above the pelvic brim were successful. We now believe that there are very few cases where open ureterolithotomy is indicated. The success rate for ureteroscopic removal of ureteric stones in this series compares favourably with blind endoscopic extraction (O'Flynn, 1980) and with ureteroscopic experience from other centres (Ford *et al.*, 1983).

The occurrence of two ureteric strictures after ureteroscopy gave rise to some concern, but in one case there was a pre-existing stricture and the second case followed open surgery. Neither stricture occurred at the sites which caused the greatest difficulty in negotiation. Nonetheless, the instrument must be used with caution and the greatest care is required when advancing the instrument up the ureter.

The incidence of complications is low (Table 2). Ureteric colic occurred in 11 patients, 8 of whom had undergone ureteroscopy for stone extraction. All episodes were short-lived and no patient was in

Table 1 Site and Success Rate of Endoscopic Stone Retrieval from the Ureter

Site of stone	*Number*	*Level reached*	*Stone removed*
Upper 1/3	3	3	3
Middle 1/3	4	2	1
Lower 1/3	13	10	6

Table 2 Complications of Ureteroscopy

Ureteric colic	11
Perforation	1
Acute retention	1
Ureteric stricture	2

hospital for more than 48 h because of colic. A ureteric perforation occurred in one case; this was recognised at the time, the ureter was splinted and the leak settled without further complication.

In our experience the main role of ureteroscopy is for the retrieval of ureteric stones, but with the development of newer instruments there is considerable potential for the future, especially with regard to the management of upper urinary tract tumours.

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The Authors

D. A. Tolley, FRCS, FRCSE, Consultant Urologist, Royal Infirmary, Edinburgh.

L. L. Beynon, FRCS, formerly Senior Urological Registrar, Royal Infirmary, Edinburgh. Now Consultant Urologist, New Cross Hospital, Wolverhampton,

Requests for reprints to: D. A. Tolley, Department of Urology, Wards 15/16, Royal Infirmary, Edinburgh EH3 9YW.

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Long-term Follow-up, Further Experience with and Modifications of the Transverse Colon Conduit in Urinary Tract Diversion

J. D. SCHMIDT, H. J. BUCHSBAUM and D. A. NACHTSHEIM

Division of Urology, Department of Surgery, University of California, San Diego School of Medicine, San Diego, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Southwestern Medical School, Dallas, USA

Summary—In the past 6 years, an additional 22 patients with extensive pelvic irradiation have had their upper urinary tracts diverted employing the transverse colon conduit. Most procedures were performed with radical cystectomy following high dose radiotherapy in patients with bladder cancer or with pelvic exenteration for recurrent cervical cancer. The operative mortality rate was unchanged at 4%. Upper urinary tracts and renal function have remained stable or improved in 88 and 95% of patients respectively. Although most conduits were constructed with refluxing ureterocolic anastomoses and without stents, the more recent procedures have employed both antireflux submucosal tunnel anastomoses and stents.

Nineteen of 25 patients diverted by this method between 1970 and 1976 have been followed for up to 155 months. All patients with recurrent or persistent malignancy have died (mean survival 44 months). Seven patients (37%) are living and well (mean survival 104 months). Upper urinary tracts remain normal in two-thirds of those with the longer follow-up.

Major complications requiring additional surgery continue to occur in one-third of this highly selected group of patients in whom the transverse colon conduit remains the preferred diversionary technique.

The ileal conduit is considered the standard method of supravesical diversion for most patients. However, the problems related to the use of tissue damaged by irradiation in patients requiring diversion have led to the search for alternatives, preferably in the non-irradiated intestinal tract (Mogg, 1967). For example, within the past decade the transverse colon conduit has been used increasingly for patients with urological and gynaecological pelvic malignancies or with complications of radiotherapy (Altwein and Hohenfellner, 1975; Morales and Golimbu, 1975). The authors' initial experience with this form of diversion began in 1970 (Schmidt *et al.*, 1975, 1976). The current series reflects our more recent experience and details some modifications of the original technique.

Patients and Methods

Between October 1976 and September 1983 transverse colon conduit urinary diversions were performed in 22 patients. One patient with prostatic cancer had a unilaterally non-functioning kidney which was not diverted. Thus a total of 43 ureters were diverted. Sixteen patients were female and 6 male. Their ages ranged between 34 and 76 years (mean age 59). All patients have been followed up for an average of over 20 months (range 6 days–50 months). The one operative mortality accounts for the short follow-up of one patient. The indications for urinary diversion are shown in Table 1.

Pre-operative intravenous urograms were normal in 18 patients with 36 ureters. Two patients demonstrated bilateral hydroureteronephrosis (including one non-functioning kidney) and 2

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Table 1 Indications for Transverse Colon Conduit Urinary Diversion (22 Patients, Current Series)

With radical cystectomy for bladder cancer following high dose radiotherapy	12
With pelvic exenteration for recurrent cervical cancer following irradiation	7
For complications of pelvic radiotherapy (cancers of prostate and cervix)	3

patients had unilateral obstruction. Pre-operatively, the serum creatinine concentration was normal in all 22 patients.

The surgical technique of transverse colon conduit urinary diversion was essentially as described by Schmidt *et al.* (1975, 1976). Sufficient conduit length was obtained to allow formation of an everting or "rosebud" stoma. Twenty-nine ureters (16 right and 13 left) were reimplanted into the conduit in an end-to-side refluxing manner; 5 were reimplanted (2 right and 3 left) by an antirefluxing submucosal tunnel technique (Leadbetter and Clarke, 1955). The method of ureterocolic anastomoses in 9 ureters could not be ascertained from medical record reviews.

Ureteric stents were used post-operatively for drainage in 10 patients (20 ureters) but were not used in 8 patients (16 ureters). The use of stents could not be ascertained in the remaining 4 patients.

Lastly, medical records of the original series of 25 patients (Schmidt *et al.*, 1975, 1976) diverted via transverse colon conduit between 1970 and 1976 were reviewed. Available information consisted of survival with or without malignancy, death with or without malignancy, status of upper urinary tracts at last follow-up, the occurrence of significant complications and operative procedures thought to be secondary to the diversion operation.

Results

Current Series

One patient, a 53-year-old female with extensive cervical carcinoma, died on the sixth post-operative day. Seven additional patients have died as a result of their malignancy from 4 to 25 months after operation. The average length of survival for this group is 13.5 months. Thirteen patients (62%) are alive without current evidence of disease 1 to 50 months after operation, with an average survival of 24.2 months. One patient has been lost to follow-up.

Intravenous urograms showed stable or improved upper urinary tracts in 15 to 17 evaluable patients (88%). Two patients (12%) demonstrated further deterioration, and the post-operative upper tract status is unknown in 5. Of 5 ureterorenal units obstructed pre-operatively and diverted, 3 (60%) have improved or stabilised. The remaining 2 units (40%) have continued to deteriorate. One obstructed, non-functioning kidney in the patient with prostatic cancer was not diverted.

Significant complications of the urinary diversion occurred in 6 patients (27%) and were treated 3 to 22 months post-operatively (Table 2). Each of these complications required operative intervention. Parastomal hernia or prolapse was identified in 2 women who were otherwise well and free of disease following radical cystectomy and conduit diversion for invasive bladder cancer. One of these women had an antirefluxing ureterocolic anastomosis on one side and a refluxing anastomosis on the other (Figs 1 and 2).

Table 2 Major Complications of Transverse Colon Conduit Urinary Diversion (22 Patients, Current Series)

Complications (months post-op.)	*Management*
Parastomal hernia (17)	Repair
Parastomal hernia and prolapse (22)	Repair, revision of conduit
Ureteric obstruction, ischaemia (3)	Revision of anastomosis
Ureteric obstruction, ischaemia (6)	Nephroureterectomy
Ureteric obstruction, recurrent tumour (6)	Loop nephrostomy
Stomal prolapse (3)	Repair pending

A 40-year-old female had her left ureterocolic anastomosis revised 3 months after pelvic exenteration for recurrent carcinoma of the cervix. No tumour was identified at the secondary procedure and she is alive and disease-free 18 months after diversion. A 69-year-old woman developed marked left ureteric obstruction 6 months after radical cystectomy and transverse colon conduit diversion and a left nephroureterectomy was performed. The pathology report revealed ischaemic stenosis with no evidence of malignancy, but she died of metastatic bladder cancer 24 months after her diversion.

Finally, a 65-year-old man with radiation cystitis following treatment for prostatic cancer developed recurrent obstruction of his right ureterocolic anastomosis 6 months after diversion. Because of non-function of the opposite kidney only a unilateral

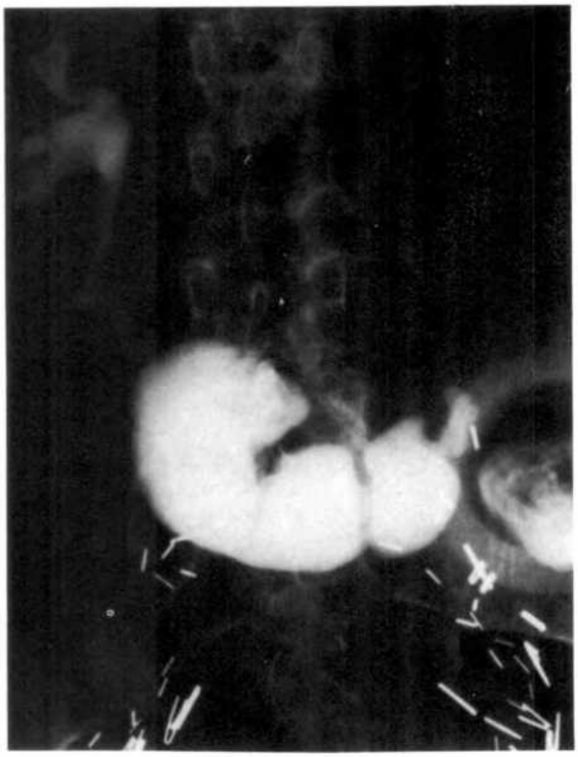

Fig. 1 Post-operative loopogram demonstrates ureteric reflux only into right upper tract. This patient had refluxing ureterocolic anastomosis on right but antirefluxing anastomosis on left. Mildly redundant colonic conduit related to prolapse and parastomal hernia required surgical revision

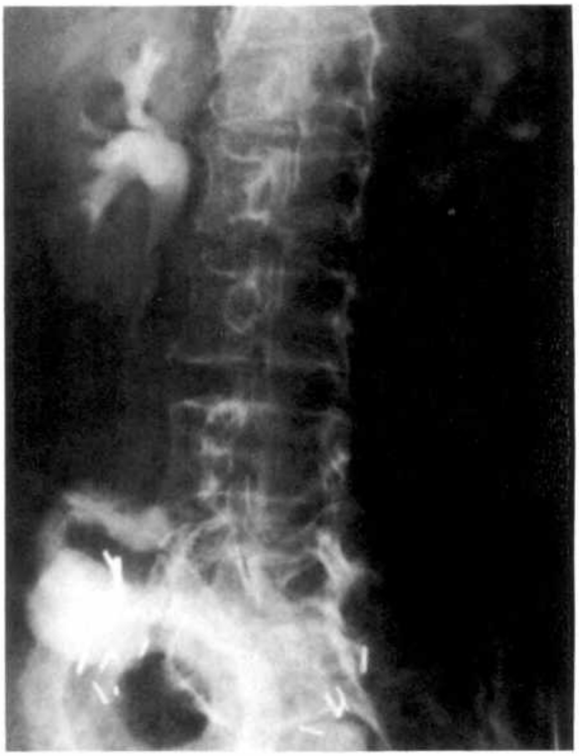

Fig. 2 Intravenous urogram of same patient as in Figure 1. Normal upper tracts are demonstrated.

diversion had been performed. At re-exploration, the recurrent obstruction was found to be due to severe retroperitoneal involvement with prostatic cancer and a right loop nephrostomy was inserted. He died of metastatic prostatic cancer 20 months after his transverse colon conduit diversion.

Original Series

Of the 25 patients diverted by transverse colon conduits between 1970 and 1976, 19 were available for assessment. The remaining 6 died (5 with persistent cancer) within 14 months of their surgery (Schmidt *et al.*, 1975, 1976). The 19 patients (6 men and 13 women) have been followed up from 5 to 155 months (mean 65 months). Eleven (58%) were alive at the time of our last review but have since died of their underlying malignancy 5 to 96 months following diversion. The mean survival in this group was 44 months. At their last examination the upper urinary tracts were normal in 7 patients (64%), hydronephrotic in 3 (27%) and unknown in 1 (9%). An additional patient (5% of the original series) diverted because of problems related to treatment of cervical carcinoma, died of atherosclerotic cardiovascular disease 29 months postoperatively. She had had normal upper urinary tracts and was free of recurrent malignancy.

Seven of the 19 patients (37%) are alive without evidence of disease 38 to 155 months after diversion (mean survival 104 months). The upper urinary tracts were normal in 2 patients (29%), contained calculi in 2 (29%), and were unknown in 3 (42%).

The long-term complications occurring in 8 patients (42%), most of which required additional surgery, are listed in Table 3. Thus the overall incidence of significant complications was 34%.

Discussion

The operative mortality rate in this series was 4% and this compares favourably with the 4% also noted in our original series (Schmidt *et al.*, 1976). This incidence is consistent with that reported in radical cystectomy in general and is compatible with the high-risk group that this patient population represents.

Similarly, the number of secondary procedures required in the current series (27%) is consistent with pelvic irradiation and malignancy and the advanced age of several patients. In spite of these factors, the improvement or stability of upper tracts seen on intravenous urography in 88% and the improvement or stability of renal function in 95% suggest that the transverse colon conduit is a good method of upper tract diversion in high-risk patients. In the 62% of patients in the series who are alive without evidence of recurrent disease are included 4 patients requiring secondary surgery (3 for parastomal hernia and prolapse and 1 for benign obstruction of a ureterocolic anastomosis).

The high rate of complications (42%) in the original series (Table 3) may reflect the number of patients free of tumour and thus at greater risk of developing problems related to prolonged survival. Our 2 longest surviving patients (155 and 127 months) have developed left renal calculi. Both had refluxing ureterocolic anastomoses performed.

Table 3 Long-term Complications and Surgical Procedures in Original Series of Transverse Colon Conduits (25 Patients with 19 at Risk)

Complications (months post-op.)	*Management*
Patients alive (NED* (7)	
Ureterocolic obstruction, renal calculus (85)	Revision of anastomosis
Parastomal hernia (39, 103)	Repair
Staghorn calculus with poor function (153)	—
Patients dead of malignancy (11)	
Stomal prolapse (8)	Repair
Bilateral ureteric obstruction, recurrent tumour (5)	Nephrostomies
Recurrent ureteric fistula (42)	Nephrectomy
Parastomal and incisional hernias (24)	—
Patient dead NED* (1)	
None	—

* NED = No evidence of disease Total 8/19 = 42%

Beckley *et al.* (1982) reported 30 patients with significant pelvic irradiation who were diverted using the transverse colon conduit and a conjoined ureterocolic anastomosis.

Sigmoid and transverse colon conduits were used almost equally in a series of 50 patients with pelvic malignancies (most gynaecological) reported by Schlesinger *et al.* (1979).

Orr *et al.* (1982) reported their experience in 119 patients undergoing pelvic exenteration, mostly for recurrent cervical cancer following irradiation. The transverse colon was used for the conduit in only 16 patients and the ileum was used in 97. All ureteric intestinal anastomoses were refluxing but stents were employed, as were staplers for formation of the conduit. Although early pyelonephritis occurred with equal frequency in ileal and transverse colon conduit patients, late pyelonephritis was seen only with ileal conduits. Similarly, 10 urinary fistulas and/or pelvic abscesses occurred, all in patients with ileal conduits. Two of these women were reoperated upon and transverse colon conduits performed. Stomal revisions have been required only in patients with ileal conduits. The author stated that "the use of a segment of unirradiated bowel (transverse colon) constitutes the preferred method of supravesical diversion in patients undergoing a pelvic exenteration."

An antirefluxing submucosal ureterocolic anastomosis using the non-irradiated colon may prevent long-term urinary infection and ascending

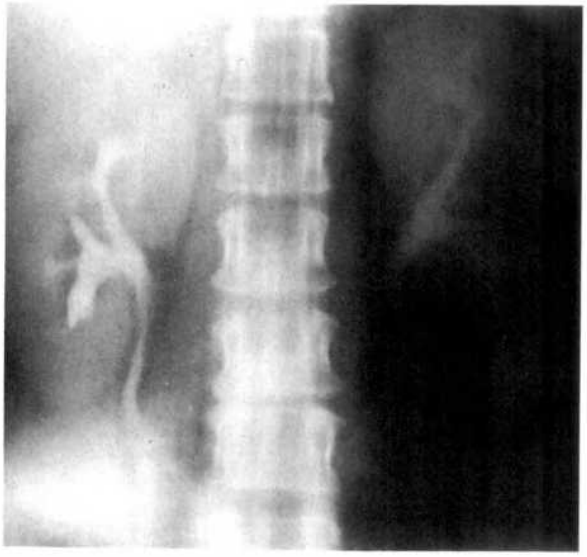

Fig. 3 Nephrotomogram performed 6 days after radical cystectomy and transverse colon conduit diversion using antireflux technique bilaterally but without diverting stents. Left-sided forniceal extravasation and swollen kidney correlated with patient's acute left flank pain and fever. Conservative treatment used successfully.

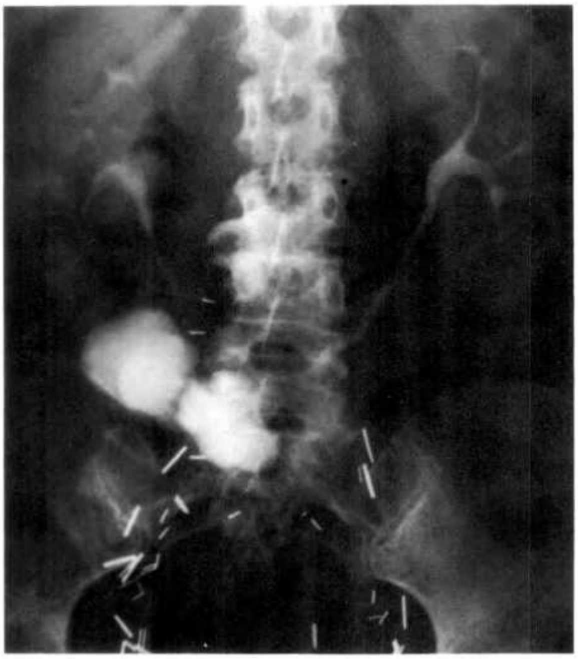

Fig. 4 Follow-up intravenous urogram of same patient as in Figure 3. Normal upper tracts are demonstrated; loopogram revealed no reflux.

pyelonephritis and also maintain the anatomical integrity of the upper urinary tract (Althausen *et al.*, 1978; Richie, 1979). An interesting aspect of this technique is seen in Figures 1 to 4.

With the addition of the current series, the authors have used transverse colon conduit urinary diversion in 47 patients, 33 of whom were women. Most patients had either bladder or cervical carcinoma. Indications for the operation fall into three categories: (1) as planned treatment for the cure of malignancy (27 patients); (2) complications of pelvic irradiation with or without malignancy (17); (3) as palliation for ureteric obstruction caused by inoperable cancer (3).

In general, we favour the use of the transverse colon conduit for primary supravesical urinary diversion and do not reserve it as a "salvage" procedure because we can incorporate an antirefluxing ureterocolic anastomosis. However, only longer experience with more patients will solve the dilemma of "which segment for which patient".

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The Authors

J. D. Schmidt, MD, Professor of Surgery and Head of Division of Urology, University of California, San Diego School of Medicine.

H. J. Buchsbaum, MD, Professor of Obstetrics and Gynecology and Director of Gynecologic Oncology, University of Pittsburgh School of Medicine, Pittsburgh.

D. A. Nachtsheim, MD, Clinical Associate Professor of Surgery/Urology, University of California, San Diego School of Medicine.

Requests for reprints to: J. D. Schmidt, Division of Urology, H-897, Department of Surgery, University of California Medical Center, San Diego, 225 Dickinson Street, San Diego, California 92103, USA.

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Vasoactive Intestinal Polypeptide in the Hyper-reflexic Neuropathic Bladder

R. B. KINDER, J. M. RESTORICK and A. R. MUNDY

Departments of Surgery and Urology, Guy's Hospital, London

Summary—The distribution of nerves containing vasoactive intestinal polypeptide (VIP) in the hyper-reflexic neuropathic bladder was investigated using immunocytochemistry and radioimmunoassay. Biopsy specimens were taken from the bladders of 21 patients with urodynamically proven detrusor hyper-reflexia and from 20 control patients with no urodynamic abnormality. The results showed a reduction in the number of VIP immunoreactive nerves and a reduction in VIP concentration in the hyper-reflexic bladder when compared with control samples.

Detrusor hyper-reflexia is a major cause of incontinence in a number of neurological conditions affecting the lower urinary tract. While the diagnosis of hyper-reflexia is usually straightforward, the long-term management of such patients remains a problem. A pharmacological approach to treatment is successful in many cases but not all. A better understanding of the mechanisms involved in controlling detrusor function and the pathological changes occurring as a result of neurological disease should lead to an improvement in the treatment of these patients.

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide which was first isolated from porcine duodenum by Said and Mutt (1970). It is widely distributed in both the central and peripheral nervous systems and exhibits a number of features characteristic of neurotransmitters (Said *et al.*, 1980). VIP nerves are abundant in the human bladder—particularly in the detrusor muscle layer—and are significantly reduced in idiopathic detrusor instability (Gu *et al.*, 1983b). The number and distribution of these nerves suggest a modulatory role for VIP in the control of bladder function.

In the present study, immunocytochemistry and radioimmunoassay have been used to study the distribution of VIP-containing nerves and the concentration of VIP in the bladders of patients with detrusor hyper-reflexia due to a known neurological disease.

Materials and Methods

Biopsies were taken by transurethral resection from the posterolateral wall of the bladder of 21 patients with detrusor hyper-reflexia secondary to a number of causes (Table) and from 20 patients undergoing endoscopic surgery for low grade, low stage carcinoma of the bladder or other problems. There were 10 women and 11 men in the hyper-reflexic group with an age range of 17 to 78 years (mean 41 years), and 11 women and 9 men in the control group with an age range of 20 to 68 years (mean 51 years). Control patients had no urodynamic symptoms, a normal voided volume chart, a normal flow rate and no residual urine.

Table Causes of Detrusor Hyper-reflexia

Multiple sclerosis	11
Spina bifida	3
Spastic paraplegia of unknown aetiology	3
Brain stem injury	1
Shy Drager syndrome	1
Spinal cord tumour	1
Lumbar disc lesion	1
Total	21

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The biopsy specimens were prepared for staining with haematoxylin and eosin (H and E), for incubation with antiserum to VIP, and with antiserum to a general neuronal marker, neuron specific enolase (NSE), as described previously (Gu *et al.*, 1983a). In addition, two samples were incubated with antiserum to an acid brain protein S100 to provide a marker for Schwann cells (Moore, 1982). A blind assessment of the immunocytochemical results was carried out by two independent observers. The number and distribution of the immunoreactive nerves in the lamina propria, muscle layer and around the blood vessels were assessed separately.

Specimens adjacent to those used for immunocytochemistry were snap frozen and stored at 70°C in liquid nitrogen prior to extraction for radioimmunoassay (Gu *et al.*, 1983a).

Results

There were no significant differences on H and E staining between normal and abnormal bladders.

VIP, NSE and S100 immunoreactive nerves were seen in both the control samples and those from hyper-reflexic bladders. There was, however, a marked decrease in the intensity of staining and in the density of VIP immunoreactive nerves in hyper-reflexic bladders (Fig. 1) compared with the controls (Fig. 2). This decrease was more pronounced in the muscle layer than in the lamina propria and around the blood vessels. There was also a minimal decrease in the NSE-immunoreactive nerves, while S100-immunoreactive nerves showed an increase in the hyper-reflexic bladders.

Mean concentrations ±SEM for VIP measured by radioimmunoassay were 36.52 ± 4.8 pmol/g of tissue in the control bladders, and 6.22 ± 0.68 pmol/g in the hyper-reflexic bladders. This difference was statistically significant ($P < 0.001$).

Discussion

VIP-containing nerves have been found in the lower urinary tract in several mammalian species, and while considerable species variation in their distribution makes extrapolation to humans difficult (Alm *et al.*, 1980), a rich supply of VIP-ergic nerves has been found in the detrusor of man (Gu *et al.*, 1983a). The origin of such nerves is unclear, but VIP immunoreactive cell bodies have been found in the hypothalamus (Larsson *et al.*, 1976), hypogastric ganglia (Hökfelt *et al.*, 1978) and local ganglia in the genitourinary tract (Alm *et al.*, 1980; Gu *et al.*, 1983b).

In the present study, patients with hyper-reflexic bladder dysfunction were found to have a marked reduction in the number of VIP-containing nerves in the detrusor. The finding that the total number

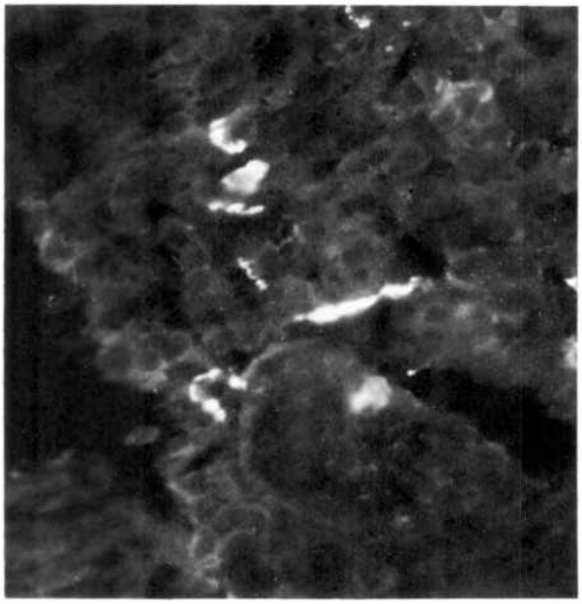

Fig. 1 VIP immunoreactive nerves in the detrusor muscle from a patient with detrusor hyper-reflexia.

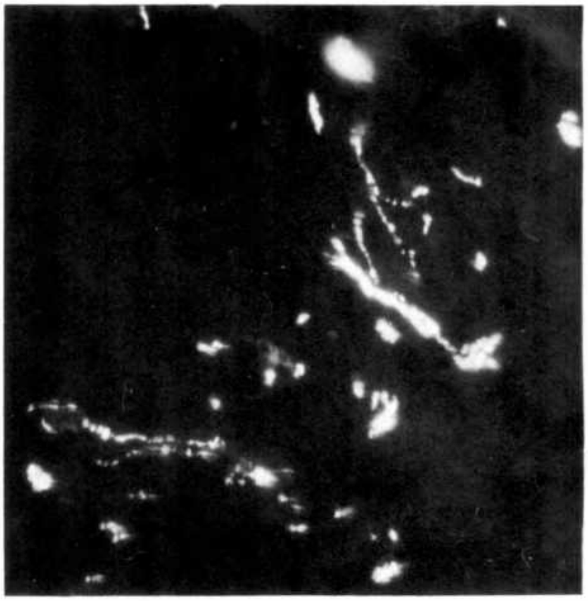

Fig. 2 VIP immunoreactive nerves in the detrusor muscle from a normal bladder.

of NSE-immunoreactive nerves was only slightly decreased, while S100-immunoreactivity was slightly increased, suggests a specific loss of VIP nerves in the bladder as a feature of the neuropathy with some attempt at regeneration.

It has been suggested that the abnormality in the unstable bladder is due to a relative overactivity of a non-cholinergic, non-adrenergic system of excitatory nerves to the bladder (Sjögren *et al.*, 1982). If this suggestion is extended to the hyper-reflexic bladder it could be postulated that the reduced concentration of VIP found in the present study was a result of attempted inhibition of this hypothetical system by an equally hypothetical inhibitory peptidergic system; in other words, that the reduced concentration of VIP was due to exhaustion of VIP from a normal complement of nerves rather than to a reduction in the number of nerves. However, the fact that treatment with anticholinergic drugs is so often successful in these patients makes this interpretation unlikely. Furthermore, in detrusor instability at least, correction of the urodynamic disorder by whatever means has led to a return of VIP concentration and the number of VIP immunoreactive nerves to normal without, necessarily, a return of the voiding frequency to normal (Mundy, 1984). It would therefore seem that a primary depletion of VIP-immunoreactive nerves is the more likely explanation for the findings of this study.

A number of pharmacological actions of VIP have been described, including the relaxation of vascular and non-vascular smooth muscle (Fahrenkrug and Emson, 1982). More recently it has been shown that VIP causes relaxation and inhibition of the spontaneous activity of human detrusor muscle strips (Kinder and Mundy, 1985). The present study provides further support for the suggestion that VIP-containing nerves might play a role in the modulation of detrusor activity in health and disease.

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The Authors

R. B. Kinder, FRCS, Lecturer in Surgery.

J M Restorick, Research Assistant.

A. R Mundy, MS, FRCS, MRCP, Senior Lecturer in Urology and Consultant Urological Surgeon.

Requests for reprints to: A. R. Mundy, Department of Surgery, Guy's Hospital, St Thomas Street, London SE1 9RT

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An Experimental Model of Detrusor Instability in the Obstructed Pig

G. N. A. SIBLEY

Department of Urology, Churchill Hospital, Oxford

Summary—Bladder outflow obstruction was produced in 18 young male pigs using either a silver ring or a silk ligature placed around the proximal urethra. Normal growth of the animals resulted in progressive obstruction. This was monitored by urodynamic studies in conscious animals, using either long-term indwelling bladder cannulae or by intermittent suprapubic catheterisation.

At urodynamic assessment 3 to 5 months later, the obstructed pigs voided at an elevated pressure and with a diminished flow rate compared with control animals. Sixty-four per cent of the obstructed pigs developed detrusor instability, with spontaneous contractions exceeding 15 cm H_2O during bladder filling; another 14% had decreased bladder compliance. In control animals the filling cystometrogram was stable, with little pressure rise during filling and no spontaneous contractions.

This animal model provides the opportunity to study the physiological changes responsible for the development of detrusor instability in the obstructed bladder. It may also be useful for evaluating new treatment regimes for detrusor instability.

In recent years it has been increasingly recognised that the response of the bladder itself to lower urinary tract obstruction plays an important role in the nature of the patient's symptoms, and that this altered bladder status may prejudice the outcome of surgery for the relief of the obstruction. In particular, detrusor instability has emerged as a major cause of frequency and urgency of micturition in obstructed patients (Bates, 1971; Turner-Warwick *et al.*, 1973); between 45 and 63% of obstructed patients have been reported to have detrusor instability on pre-operative urodynamic testing (Andersen, 1976; Abrams and Feneley, 1978; Abrams *et al.*, 1979).

Although the unstable detrusor behaviour may resolve after successful relief of the obstruction (Bates, 1971), in approximately one-third of these patients the instability will persist (Andersen, 1976; Abrams, 1978). Persistence of detrusor instability after relief of the obstruction may produce continuing symptoms and is an important contributory factor in many cases of post-prostatectomy incontinence (Fitzpatrick *et al.*, 1979; Reid *et al.*, 1980).

Despite the importance of lower urinary tract obstruction in clinical practice, the physiological changes that occur in the bladder in response to obstruction, and which may subsequently lead to such disorders in function as detrusor instability, are poorly understood. A suitable animal model that mimicked the response of the human bladder to obstruction would therefore be of value in allowing these changes to be studied in detail.

Melick *et al.* (1961) performed cystoscopy, cystography and cystometrography in young pigs and found a close resemblance to the findings in man. In addition, Hodson *et al.* (1975) and Ransley and Risdon (1978) used the pig in their investigations on vesicoureteric reflux, and studied the effects of high pressure voiding in reflux nephropathy after experimental obstruction at the level of the proximal urethra; marked hypertrophy of the bladder wall was reported to occur following obstruction in these animals.

These studies suggested that the pig would be a suitable model for producing bladder wall hyper-

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Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984. This study was awarded the Eschmann prize.

trophy similar to that seen in obstruction in man, and enable a study of the changes in bladder function that accompany this. This study reports on the methods used in establishing this model and on the urodynamic changes that were produced as a result.

Materials and Methods

Twenty-two Landrace male pigs were obtained at 8 to 10 weeks of age, when they weighed 15 to 20 kg. Obstruction was produced in 18 pigs using either a silk ligature or a silver ring placed around the proximal urethra at the upper border of the immature prostate, which lies approximately 2 cm distal to the bladder neck. Normal growth of the animal then resulted in a progressive obstruction which was monitored by urodynamic studies over a 3- to 5-month period. Four pigs underwent a sham operation without obstruction, and their subsequent urodynamic studies served as controls.

Surgical techniques

The animals were anaesthetised using either intravenous Sagatal (pentobarbitone sodium, 60 mg/ml, May and Baker Ltd) or by inhalation of a halothane/oxygen/nitrous oxide mixture; they were intubated but breathing spontaneously.

A silk ligature was used for obstruction in 7 pigs, applied around a 10 F catheter placed within the proximal urethra (the normal urethra admitted a 20 F catheter); following withdrawal, the catheter could just be reinserted whilst a larger catheter could not. Since the distal urethra of the male pig follows a spiral course that prevents upward passage of a catheter, this had to be introduced via a cystotomy that was then repaired with 2/0 Dexon.

In 11 pigs, obstruction was produced using a silver "ring" of known diameter. This ring consisted of a horseshoe of silver wire with a loop at each end; as silver is a malleable metal, the ring could be opened and slipped around the urethra and then reformed by tying the ends together with silk (Hodson *et al.*, 1975; Ransley and Risdon, 1978). A 7 or an 8 mm ring was chosen at surgery to provide a snug fit around the urethra; since the diameter of the final ring was predetermined, a cystotomy was not required.

The 4 control animals underwent a dissection around the proximal urethra similar to that of the experimental group, but without placement of a constricting ring or ligature.

All of the animals were castrated at the initial operation to render them less aggressive and easier to handle. They received 600 mg penicillin and 1 g streptomycin IM during surgery, but antibiotic prophylaxis was not given in the post-operative period.

Following urodynamic assessment 3 to 5 months after the initial operation, a full thickness biopsy was obtained from the anterior bladder wall from control and obstructed pigs to study the physiological changes that had been produced in the detrusor muscle by obstruction; the results of these studies will be reported separately. At this time, 6 of the animals obstructed with a silver ring had the ring removed. Prior to removal the urethra admitted only a 10 to 12 F catheter, but after removal the urethra could be dilated to admit a 22 to 24 F catheter. These animals underwent further urodynamic assessment 3 months later to determine the reversibility of the changes in bladder function that had been produced by obstruction.

Urodynamic assessment

Two methods were used for urodynamic assessment in conscious animals. One method involved the suprapubic insertion of a 16 gauge epidural cannula (1.1 mm external diameter, Portex Ltd) into the bladder via a 1.6 mm trocar, during anaesthesia with halothane/oxygen/nitrous oxide administered by a conical face mask. The epidural cannula was secured to the skin and connected to the pressure recording equipment. A forced diuresis was produced for bladder filling by the intravenous infusion of normal saline and injection of frusemide (20 mg IV plus 20–60 mg IM, depending on size). The pig was then woken, the animals recovered quickly from this short anaesthetic and within a few minutes were fully alert and allowed to feed from a trough. The intravesical pressure was monitored via the suprapubic cannula during several subsequent filling and voiding cycles before the cannula was removed. The voided urine was collected and an average flow rate calculated from its volume and the voiding time.

The second method used long-term indwelling bladder cannulae. At open operation, two 5 F central venous catheters, 28 inches long (Drum-cartridge catheter, Abbott Laboratories), were placed in the bladder through separate stab incisions in the dome and secured with a 2/0 Dexon purse-string suture. The cannulae were passed through a subcutaneous tunnel on to the left thorax dorsally, which was a convenient site to apply a protective dressing. Serial urodynamic studies could then be performed using one cannula for bladder filling and the other for monitoring the intravesical pressure. Normal saline at room temperature was used for filling, using a Metroset in young pigs (filling rate approximately 15 ml/min) and a standard IV infusion set in older pigs (filling rate approximately 35 ml/min).

In each method, the cannula for measuring bladder pressure was connected via a 150 cm manometer line (Portex Ltd) to a Bell and Howell type 4-422 physiological pressure transducer, placed approximately level with the animal's symphysis pubis. After amplification, the pressure was recorded on one channel of a Servoscribe 2s two-channel polygraph. Pressures were expressed in cm H_2O, the pressure transducer being calibrated at each study against a vertical column of water. Because of the difficulty in ensuring that the transducer was positioned at exactly the same level in each pig, changes in the intravesical pressure were measured rather than the absolute values. The pressures recorded were the rise in pressure during filling and the peak voiding pressure; the latter was measured as the total increase in pressure from the start of the filling cystometrogram to the maximum value achieved during voiding, thus incorporating any rise that had occurred during filling.

Urine bacteriology

Urine specimens were obtained for culture at the start of the experiment by direct bladder puncture at operation, and later specimens were obtained at the time of operative biopsy or by percutaneous bladder puncture when inserting a suprapubic cannula for urodynamic studies.

Positive cultures were assessed in a semi-quantitative fashion and the nature of the infecting organisms determined by standard bacteriological methods. Profuse or moderate growths of faecal organisms were regarded as indicative of infection, whilst light or moderate growths of skin organisms were regarded as contaminants.

Results

Five of the obstructed animals developed acute retention of urine 3 to 8 days after operation. One animal died following bladder rupture. In the other 4 animals the obstructing ring or suture was removed and a less marked constriction created.

Three to 5 months after the initial operation, urodynamic studies were performed on 14 of the obstructed pigs and all 4 control animals. One of the obstructed animals was in chronic retention of urine with ineffective voiding; in the other 13 animals voiding occurred at a significantly higher bladder pressure and with a significantly reduced urine flow rate than in the control animals (Table). The voided volumes were also significantly less in obstructed animals (Table), indicating a decrease in the functional bladder capacity. The residual urine could not be measured accurately with the cannulae used, but the finding of a large volume of residual urine in some obstructed pigs at the time of bladder biopsy suggested that the decrease in voided volume was due to incomplete bladder emptying.

Table Pressure-flow Data from Urodynamic Studies Performed 3 to 5 Months after Proximal Urethral Obstruction in 13 Pigs, Compared with Control Data from 4 Pigs that Underwent a Sham Operation without Obstruction

	Control *(4 pigs)*	*Obstructed* *(13 pigs)*
Peak voiding pressure (cm H_2O)	22 cm, n = 10 (16–30 cm)	62 cm, n = 41 (35–115 cm)
Average urine flow rate	8.7 ml/s, n = 14 (6.7–11.5 ml/s)	2.2 ml/s, n = 31 (1.2–3.5 ml/s)
Average voided volume	364 ml, n = 14 (120–980 ml)	168 ml, n = 31 (45–620 ml)

Average values are given, with the range of values in brackets. The values in obstructed pigs were all significantly different from the control values ($P < 0.001$).
n = number of recordings.

In addition to these differences during the voiding study, marked differences between the obstructed and control animals were seen during the filling phase of the cystometrogram. Figure 1 illustrates the filling cystometrogram and accompanying voiding study from a control pig. In control animals there was little rise in bladder pressure during the filling cystometrogram, the average rise being 1 cm H_2O (range 0–4 cm H_2O, n = 10 recordings). No spontaneous contractions were seen during this filling phase (the spiky appearance being due to movement artefact), so that such bladders were described as "stable". Although the animals often fed throughout filling, they usually stopped feeding during voiding.

In contrast, in 9 of the 14 obstructed animals (64%) there were spontaneous bladder contractions exceeding 15 cm H_2O during the filling cys-

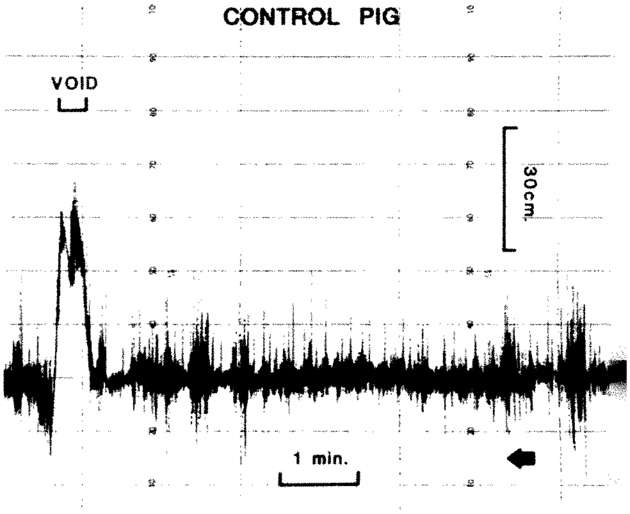

Fig. 1 Urodynamic study from an unobstructed control pig. The filling cystometrogram is stable, with little pressure rise during filling and no spontaneous contractions (the spiky appearance is an artefact due to movement during feeding). Study performed 3 months after a sham operation on the proximal urethra.

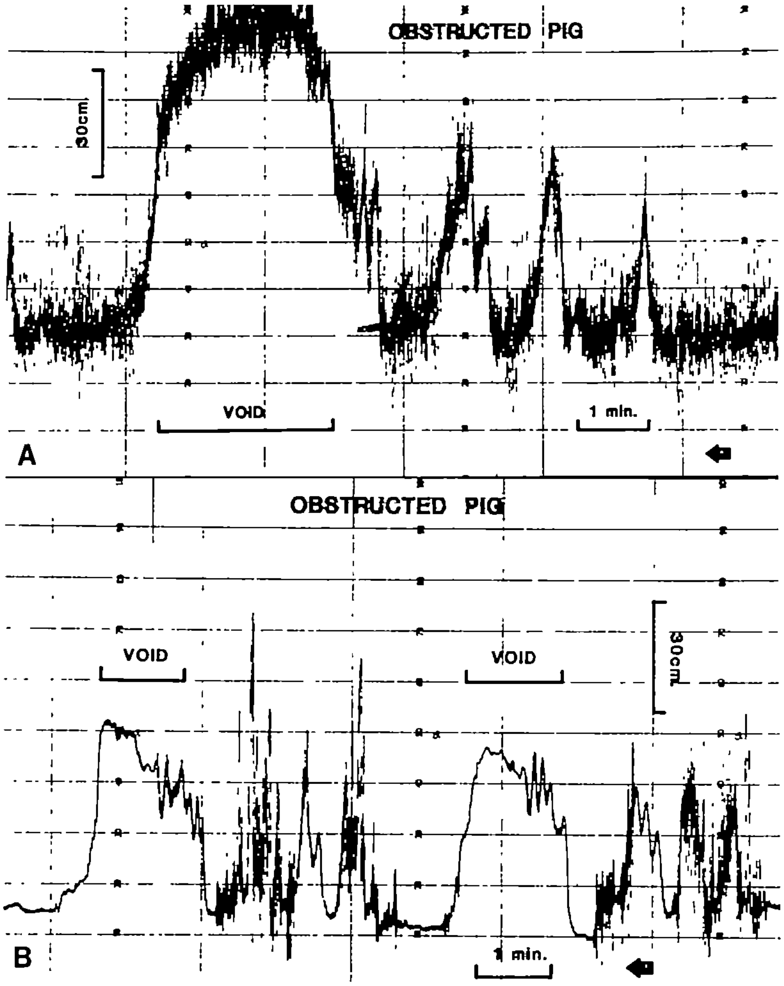

Fig. 2 Urodynamic studies from 2 obstructed pigs (A,B) with detrusor instability During the filling cystometrogram, spontaneous bladder contractions exceeding 15 cm H_2O occurred which were not accompanied by voiding. Subsequent voiding was at an elevated pressure and with a reduced urine flow rate. Study *B* illustrates the similarity between successive filling and voiding traces in the same animal Studies performed 3 months after proximal urethral obstruction.

tometrogram. Figure 2 illustrates the tracings from 2 animals showing this behaviour. During these contractions, which were sometimes up to 1 min in duration, there was either no leakage or leakage of only a few drops of urine; the animal often became restless during the contractions but did not necessarily stop feeding. Although the intra-abdominal pressure was not monitored, these spontaneous bladder contractions were quite distinct from the effects of grunting and straining, which produced transient pressure rises lasting a few seconds only. Bladders showing this pattern were described as "unstable" (see Discussion). In some of these animals with an unstable cystometrogram, the bladder pressure returned towards the baseline between contractions, whilst in others the contractions were superimposed on a steadily rising intravesical pressure. The average pressure rise during filling in this group was 23 cm H_2O (5–62 cm H_2O, n = 27).

In 2 of the remaining 5 obstructed pigs (14% of the total number) there was a decrease in the bladder compliance alone, with a progressive pressure rise exceeding 15 cm H_2O during bladder filling (Fig. 3). The average pressure rise during filling in these 2 animals was 55 cm H_2O (45–63 cm H_2O, n = 4) and voiding occurred with little or no additional pressure rise.

In 2 other obstructed animals (14% of the total), the cystometrogram was stable, with a pressure rise averaging only 1 cm H_2O (0–5 cm H_2O, n = 10) during filling and no spontaneous contractions; this was in spite of elevated voiding pressures and

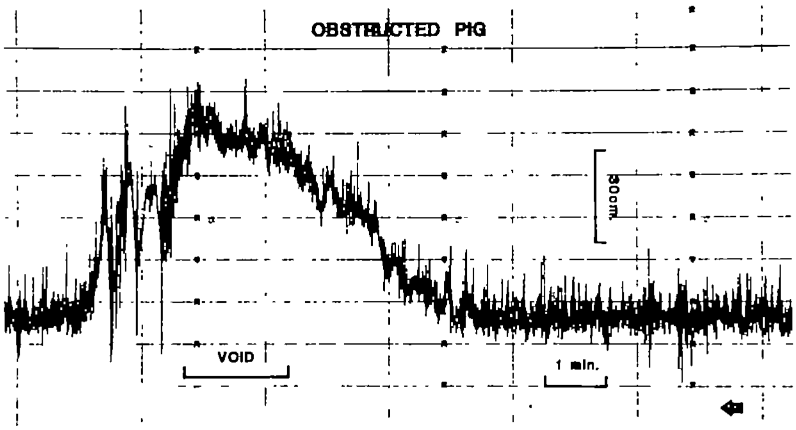

Fig. 3 Urodynamic study from an obstructed pig with decreased bladder compliance. There was a progressive pressure rise during filling to a pre-micturition value of 55 cm H_2O, and voiding occurred with little additional pressure rise. Study performed 4 months after proximal urethral obstruction.

diminished urine flow rates that were not significantly different from the values seen in the unstable pigs, suggesting a similar degree of obstruction in each group.

The remaining obstructed pig had chronic retention of urine and was not included in any of the above three groups.

The incidence of urinary tract infection in obstructed pigs was 47% compared with infection in 1 of the 4 control animals (25%). Infection was seen in animals belonging to each of the urodynamic groups and did not appear to be causally related to an unstable cystometrogram.

At the time of operative bladder biopsy, the bladder wall was noted to be thicker in the obstructed animals than in controls, with up to a 4-fold increase in thickness.

In the group of 6 pigs undergoing relief of obstruction, 4 had developed detrusor instability whilst obstructed and 2 were urodynamically stable. At further assessment 3 months after removal of the constricting silver ring, both of the stable animals maintained a stable cystometrogram; the peak voiding pressure and urine flow rate had returned to normal in both animals, indicating complete relief of their obstruction.

Of the 4 pigs with obstructive detrusor instability, 2 had reverted to stability by 3 months, whilst the other 2 remained unstable. The voiding parameters in the 2 animals reverting to stability indicated that satisfactory relief of the obstruction had been achieved. However, in both of the animals with persistent instability the peak voiding pressure remained elevated despite an increase in the flow rate towards the normal value; residual obstruction could therefore not be excluded as the cause of the persistent instability.

Discussion

The experimental techniques used in this study in the pig were successful in producing a significant degree of bladder outflow obstruction. An important additional feature was the development of spontaneous contractions exceeding 15 cm H_2O during bladder filling in nearly two-thirds of the obstructed pigs. It is, of course, not possible to determine whether such contractions were voluntary or involuntary in this animal model. Nevertheless, a description of such bladders as "unstable" would appear justified, in view of the marked similarity to the pattern often seen in human patients with combined bladder outflow obstruction and detrusor instability. In addition, no such contractions were seen during urodynamic studies either in young pigs prior to obstruction or in the control pigs. In clinical practice, the International Continence Society (1976) recommended a pressure rise exceeding 15 cm H_2O during bladder filling as an indicator of detrusor instability, and this value was therefore used here, rather than choosing a different arbitrary value in pigs.

Such cystometric changes were not reported in two previous studies on vesicoureteric reflux in obstructed pigs (Hodson *et al.*, 1975; Ransley and Risdon, 1978), but in both of these studies early relief of the obstruction was performed if either the micturition habits changed, with the development of frequency and the voiding of small quantities of urine, or if the bladder was increasing in size with residual urine. Thus the obstruction may have been relieved before instability could develop.

However, Jørgensen *et al.* (1983) reported spontaneous contractions during cystometry under general anaesthesia in 6 of 7 female pigs 10 weeks after proximal urethral obstruction, although no such contractions were seen in unobstructed control animals. These contractions were of smaller amplitude (mean amplitude 7.5 cm H_2O, range 5–13 cm H_2O) than in the present study, but the authors chose to regard any contraction in excess of 5 cm H_2O as indicative of detrusor instability. Despite this difference in the criteria for defining instability, Jørgensen's study nevertheless also demonstrated that the pig bladder responds to obstruction in a similar fashion to the human bladder.

Detrusor instability has not been reported following experimental obstruction in other species, although the methods of evaluating bladder function in previous studies usually involved measuring the intravesical pressure rise on pelvic nerve stimulation in anaesthetised animals (Mayo and Hinman, 1976; Mattiasson and Uvelius, 1982) rather than by filling cystometry and pressure measurements during spontaneous voiding in conscious animals. Arbuckle and Paquin (1963) did perform urodynamic assessment using urethral catheters in conscious rabbits over a 3-month period after experimental bladder neck obstruction, but found little difference in the voiding pressure or urine flow rate compared with control animals despite marked structural changes in the obstructed bladders.

Poorly sustained "autonomous" bladder contractions were found during cystometry in conscious female dogs after division of the pelvic nerves, and more pronounced reflex or "automatic" contractions after transection of the spinal cord (Jacobson, 1945); similar autonomous bladder contractions occurred during cystometry in anaesthetised cats after bilateral section of the pelvic nerves or sacral roots (Carpenter and Root, 1951). However, the obstructed pig bladder behaves in a quite different fashion from these neurogenic bladders, since a sustained voiding contraction is present at the end of bladder filling in obstruction but not following neurological lesions.

The cause of the decreased bladder compliance seen in 2 of the obstructed pigs is not clear, but it could be due to changes in the visco-elastic properties of the hypertrophied bladder wall or, alternatively, be the result of a sustained contraction of the detrusor muscle. Experimental studies suggest that bladder tone during filling cystometry in the normal bladder is not nerve-mediated but is due to the physical and physiological properties of the bladder wall (Tang and Ruch, 1955), but the mechanisms involved when the bladder compliance is reduced require further investigation.

In contrast to the presence of detrusor instability in nearly two-thirds of the obstructed animals, 2 pigs (14%) maintained a stable cystometrogram with little pressure rise during filling. The finding that the voiding pressures and flow rates were similar in these stable animals to the corresponding values in the unstable pigs indicates that instability is not related solely to the severity of the obstruction.

Although nearly half of the obstructed pigs developed urinary tract infection, the presence of infection did not appear to be causally related to the development of detrusor instability. In addition, infection was present in many of the obstructed pigs studied by Hodson *et al.* (1975) (54% infected) and Ransley and Risdon (1978) (47% infected), yet none of these animals had unstable cystometrograms.

The finding that the unstable detrusor behaviour in obstructed pigs could revert to normal after relief of the obstruction was further evidence of the similarity of this model to the condition found in man. However, in the animals with persistent instability it was not possible to exclude residual obstruction as the cause, and study of a larger group is necessary to determine whether instability will persist in this model after complete relief of obstruction.

Thus experimental bladder outflow obstruction in the pig proved to be a good model for this condition in man. The author has used the model to study the physiological changes that occur in the detrusor muscle in response to obstruction and which lead to such disorders in function as detrusor instability (Sibley, 1984), and it should be of value in further studies on this problem. It would also be possible to use this animal model to investigate the influence of factors such as the duration and severity of obstruction on the subsequent reversibility of obstructive detrusor instability. In addition, the model offers the prospect of assessing new regimes for the treatment of patients with obstructive detrusor instability, for example those with persistent instability after operation, and may also be useful in evaluating treatment for the other categories of detrusor instability encountered in clinical practice.

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The Author

G. N A Sibley, FRCS, Research Registrar, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ

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Cis-platin and Methotrexate in the Treatment of Transitional Cell Carcinoma of the Urinary Tract

J. CARMICHAEL, M. A. CORNBLEET, R. H. MacDOUGALL, S. G. ALLAN, W. DUNCAN, G. D. CHISHOLM and J. F. SMYTH

Departments of Clinical Oncology and Surgery, Western General Hospital, Edinburgh

Summary—Nineteen patients with recurrent or metastatic transitional cell carcinoma of the urinary tract were treated with a 3-weekly combination of methotrexate 200 mg/m^2 as a 24-h infusion with folinic acid rescue and cis-platin 100 mg/m^2. An objective response rate of 68% was obtained, with 4 patients (21%) achieving complete remission. Pulmonary disease and lymph node metastases were particularly sensitive to this therapy. The median duration of response was 21 weeks with a median survival of 54 weeks in the responding patients. This regimen warrants further investigation in the treatment of invasive bladder carcinoma.

Several drugs have been shown to be effective as single agents in the treatment of transitional cell carcinoma of the urinary tract (TCC). Cis-platin (DDP) is generally considered the most active agent so far identified, with responses of 33 to 36% in advanced disease (Yagoda *et al.*, 1976; Soloway *et al.*, 1981) and 57% in previously untreated patients (Yagoda *et al.*, 1976). Methotrexate (MTX) has been used widely in TCC, although the dosage, route and frequency of drug administration have varied considerably, leaving the optimum schedule undefined. Turner *et al.* (1977) reported an overall response rate of 38% in 61 patients, although a 53% response rate was achieved in patients receiving a minimum of 100 mg every 2 weeks. The median duration of response was 4 to 6 months in these studies.

Combination chemotherapy has been somewhat disappointing and a number of studies showed no improvement in response rate with the addition of cyclophosphamide and adriamycin to DDP (Yagoda, 1979). Nevertheless, in view of its predictable and manageable toxicity, and relative efficacy for this disease, MTX is potentially a good drug for incorporation into combination regimens. However, the combined use of MTX with DDP is potentially more nephrotoxic. In addition, transient tubular dysfunction following DDP therapy could lead to impaired renal excretion of MTX, causing prolonged elevation of plasma levels and increased toxicity.

Patients and Methods

Nineteen patients with recurrent or metastatic TCC of the bladder, ureter or renal pelvis were entered into the study between December 1980 and January 1984. These patients had not received prior chemotherapy and had evaluable disease in previously non-irradiated sites (Table 1). Pre-treatment assessment comprised clinical examination, determination of performance status (ECOG), documentation of evaluable disease, intravenous urography, audiometry and chest X-ray. Blood tests included full blood count, urea and electrolytes, liver function tests and creatinine clearance. Isotope scans were carried out where clinically indicated. Clinical and biochemical assessments were repeated before each course of chemotherapy, which was given every 21 days, depending on blood count and creatinine clearance. Full reassessment of evaluable disease was performed after three courses, with responding patients continuing treat-

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Table 1 Details of Patients

Number of patients	19
Mean age (years)	58 5 (range 39-72)
Histology	
Grade II	2
Grade III	17
Previous therapy	
Surgery	4
Radiotherapy	
palliative	4
radical	12
Sites of disease	
Lung	11
Node	4
Bladder	7
Bone	3
Skin	1
Suprarenal	1
Pre-treatment performance status	
0	10
1	6
2	3

ment and receiving a maximum of six courses of chemotherapy.

MTX 200 mg/m^2 was administered as a 24-h infusion in 1 litre normal saline. Following this infusion 2 litres dextrose/saline were given over 24 h, with folinic acid rescue 9 mg/m^2 given 6-hourly × 8. DDP 100 mg/m^2 was prepared in 10% mannitol and given over 1 h, commencing 6 h after completion of the MTX infusion. Anti-emetics were administered prophylactically. Treatment was delayed for 1 week when the white cell count was less than 3×10^9/l or platelets less than 100,000.

In view of the potential problems resulting from renal impairment, doses were modified if creatinine clearance was less than 1 ml/s. Patients with a creatinine clearance of 0.75 to 1.0 ml/s received 75% of both drugs and those with 0.5 to 0.75 ml/s received 50% of both drugs with 72 hours' folinic acid rescue. Patients were excluded if their creatinine clearance was less than 0.5 ml/s.

Results

All 19 patients were evaluable for response. Four patients achieved complete remission and there were nine partial responders, giving an objective response rate of 68%. The results are listed in Table 2. The median duration of remission was 21 weeks, with a median survival of 54 weeks in the responders. Objective responses are illustrated on an individual basis in Table 3.

Table 4 shows the response by site of metastatic

Table 2 Response

All patients	19
Complete response (CR)	4 (21%)
Partial response (PR)	9 (47%)
Objective response (CR + PR)	13 (68%)
Response duration (median)	21 weeks
Median survival—responders	54 weeks
—non-responders	20 weeks

Table 3 Individual Patient Response

Patient	*Sites of disease*	*Response*	*Site of relapse*	*Duration of response (weeks)*	*Survival (weeks)*
JW	Lung Nodes	CR	—	180+	196+
BG	Lung	CR	Brain	38	142
TG	Bladder Nodes	CR	—	60+	63+
RB	Lung	CR	Brain	18	24
WW	Lung	PR	Lung	25	39
RKH	Nodes	PR	Liver	12	39
EA	Lung	PR	Lung	21	60
MMc	Nodes	PR	Nodes	9	54
JA	Lung Bladder	PR	Brain	104	126+
KH	Bladder Skin	PR NR	Bladder	20	26
JC	Lung	PR	Brain Lung	39	58+
AU	Lung	PR	Brain	20	34
WP	Bladder	PR	—	8+	16+
TW	Bone Bladder	NR	—	—	36
JH	Bone Lung	NR	—	—	30
JC (grade 2)	Bone Bladder	NR	—	—	20
AK	Bladder	NR	—	—	12
WW	Lung	NR	—	—	18+
OI (grade 2)	Lung	NR	—	—	18+

Table 4 Site of Disease—Response

	No Patients	*Complete response*	*Partial response*	*Objective response* (%)
Lung	11	3	5	73
Nodes	4	2	2	100
Bladder	7	1	3	57
Bone	3	0	0	0
Skin	1	0	0	0
Suprarenal	1	0	0	0

Table 5 Toxicity (WHO criteria) (%)

	Grade				
	0	*1*	*2*	*3*	*4*
Haematological	15 (79)	0	4 (21)	0	0
Nausea/vomiting	0	1	1	17 (89)	0
Renal	15 (79)	4 (21)	0	0	0
Alopecia	14 (74)	3 (16)	2 (10)	0	0
Neurotoxicity	14 (74)	5 (26)	0	0	0
*Ototoxicity	13 (68)	2 (10)	4 (21)	0	

* Non-WHO classification Grade 1—mild, audiometric only, Grade 2—moderate, symptomatic; Grade 3—severe.

disease. Metastatic deposits in the lungs and lymphatics responded best. Of 11 patients with pulmonary metastases 8 (73%) had objective responses: 3 of these showed a complete response (CR) and 5 a partial response (PR); all four patients with lymph node metastases responded (2 CR, 2 PR). Recurrent intravesical tumour responded in four patients (57%), with one achieving complete remission. Both patients who had not received pelvic irradiation responded (1 CR, 1 PR), but of those previously treated only 2/5 (40%) responded, one rapidly relapsing locally. No response was observed in patients with bony metastases. Cerebral metastases were noted in five patients (50%).

Although the median duration of response was only 21 weeks, some responding patients had durable remissions, one remaining in complete remission at 180 weeks and another at 60+ weeks. The median survival was 54 weeks in responding patients with three surviving more than 2 years; two of these remain alive, one disease-free and the other with a cerebral relapse, at 196 and 126 weeks respectively.

Side effects are listed in Table 5. Leucopenia of minor degree necessitated delayed treatment in four patients but this rapidly recovered without any infective complications. One patient had an upper gastrointestinal bleed due to ulcerative oesophagitis, not related to thrombocytopenia; otherwise there were no haemorrhagic complications. Transfusion was required in one patient for anaemia after two courses of therapy. Nausea and vomiting requiring therapy was almost universal, as expected from the use of DDP. Symptoms of mild peripheral neuropathy were noted in five patients, none of whom suffered motor deficit. Alopecia was not a significant problem, although present to some degree in 25%. High-tone nerve loss was detected in six patients, four of whom were symptomatic. Oral ulceration was a problem on one occasion. Deterioration in renal function, as measured by creatinine clearance, occurred in four patients, but all were able to tolerate full doses of chemotherapy.

Three patients entered the study with impaired renal function and received attenuated doses of both drugs. One had a creatinine clearance of 0.83 ml/s and was given 75% of both drugs; the others, with creatinine clearances of 0.5 ml/s and 0.63 ml/s, received a 50% dose of both drugs with prolonged folinic acid rescue. One patient receiving a 50% protocol dose had a short partial remission, whilst the other two did not respond. All three developed high-tone nerve damage. Despite these toxicities, this regime was acceptable to most patients and surprisingly well tolerated by the elderly.

Discussion

Despite the obvious need for effective systemic treatment for TCC, and the demonstrated activity of a number of cytotoxic drugs, the role of combination chemotherapy remains far from clear. DDP has proven activity as a single agent (Yagoda *et al.*, 1976; Soloway *et al.*, 1981), but there is no convincing evidence of increased activity when used in combination with adriamycin or cyclophosphamide (Yagoda, 1979). MTX alone has also been shown to be active (Turner *et al.*, 1977), with no demonstrable improvement in combination with vinblastine (Needles *et al.*, 1983) or adriamycin and cyclophosphamide (Tannock *et al.*, 1981). The possibility of potentiating MTX toxicity due to impaired renal excretion following DDP has probably deterred oncologists from looking at this combination. Recently, however, Kaye *et al.* (1984) reported no increase in toxicity when combining DDP and MTX when both were given at 50 mg/m^2. Alternatively, MTX analogues have been used, with Natale *et al.* (1983) reporting a 62% response rate in 13 patients treated with cis-platin and dichloromethotrexate, the latter excreted predominantly via the biliary route. In view of Turner's data (1977) suggesting increased responsiveness with higher doses of MTX, we elected to give 200 mg/m^2 in a 24-h infusion combined with high dose DDP. An encouraging 68% response rate in 19 patients was achieved with a median duration of response of 21 weeks and a median survival of 54 weeks, some of the responding patients having durable remissions. The potential complications from impaired renal excretion of MTX did not arise, the predominant toxicity being DDP-induced nausea and vomiting. Hearing loss was not uncommon, particularly in patients with abnormal renal function.

As reported previously, nodal disease was very responsive and pulmonary metastases also responded well, with a 73% response rate in 11 patients. In contrast, bony metastases in three patients showed no objective response. Recurrent disease in the bladder responded in 4/7 cases and appeared more sensitive in non-irradiated patients. Indeed the one patient to achieve a complete response had extensive local disease (T4), with biopsy-proven inguinal and supraclavicular lymphadenopathy. After 6 courses of chemotherapy he was fully investigated, including repeat cystoscopy, and in view of the bulky pelvic disease at presentation he was given X-irradiation to this area to consolidate the remission. He remains in complete remission at 60 weeks. However, the precise role for the combination of chemotherapy and radiotherapy remains unclear, although Kyriazis *et al.* (1983) recently showed potentiation of the effects of ionising radiation by cis-platin in a human bladder xenograft model.

Cerebral metastases are seldom found in bladder cancer and it is of interest that following this cytotoxic chemotherapy a common site of relapse was the brain. In 10 patients with documented relapse, five (50%) had cerebral metastases, which indicated that the natural history of the disease may have been influenced by this therapeutic regimen.

These patients were younger than average for a population with bladder cancer in the UK, their mean age of 58.5 years being almost 10 years less than that of all patients with bladder cancer referred to this department. It is recognised that they tolerate cytotoxic chemotherapy better than the older patients, although this regimen was acceptable to most, including elderly patients. It should be pointed out that 17/19 (89%) patients had poorly differentiated TCC (grade III), which is usually associated with a poor prognosis. These patients are at greater risk of developing metastases, and possibly tumour grade should be a factor in their selection for cytotoxic chemotherapy.

DDP and MTX are highly effective in the treatment of metastatic TCC, with pulmonary and soft tissue disease the most responsive. Toxicity was controllable and was remarkably well tolerated even by the elderly patients. This regimen therefore warrants further investigation in the treatment of invasive carcinoma of the bladder.

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The Authors

J. Carmichael, MRCP, Imperial Cancer Research Fund Research Fellow, Medical Oncology Unit, Western General Hospital, Edinburgh.

M. A. Cornbleet, MD, MRCP, Cancer Research Campaign Hamilton-Fairley Travelling Research Fellow, Chicago Cancer Research Center, University of Chicago, USA.

R. H. MacDougall, FRCR, FRCSE, DMRT, Consultant Radiotherapist and Honorary Senior Lecturer, Ninewells Hospital and Medical School, Dundee.

S. G. Allan, MRCP, Imperial Cancer Research Fund Research Fellow, Medical Oncology Unit, Western General Hospital, Edinburgh.

W. Duncan, FRCPE, FRCSE, FRCR, FACR(Hon), Professor of Radiotherapy, University of Edinburgh; Honorary Consultant Radiation Oncologist, Western General Hospital and Royal Infirmary, Edinburgh.

G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery, University of Edinburgh; Consultant Urologist, Western General Hospital, Edinburgh.

J. F. Smyth, MA, MSc, MD, FRCP, FRCPE, Imperial Cancer Research Fund Professor of Medical Oncology, University of Edinburgh; Consultant Medical Oncologist, Western General Hospital, Edinburgh.

Requests for reprints to: J. F. Smyth, Department of Clinical Oncology, Western General Hospital, Edinburgh EH4 2XU.

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Cystectomy for Carcinoma of the Bilharzial Bladder
126 Patients 10 Years later

M. A. GHONEIM, A. ASHAMALLA, M. A. GABALLA and E. I. IBRAHIM

Urology and Nephrology Centre, Mansoura University, Mansoura, Egypt

Summary—Our experience with 126 cases of bilharzial bladder cancer treated by radical cystectomy and followed up for at least 10 years is outlined.

The operative mortality rate was 13.5%. The 5- and 10-year survival rates were 32.6 and 23% respectively. The difference between the two figures can be attributed to mortality from natural ageing rather than recurrence of cancer. Analysis of survival figures revealed that the tumour grade was the most important prognostic factor. Most treatment failures were due to local recurrence which developed soon after treatment.

Carcinoma of the urinary bladder is the commonest solid tumour among adult males in Egypt (Makar, 1955; El-Sebai, 1961). The association between bladder cancer and urinary bilharziasis forms a distinct clinicopathological pattern. Most patients are seen at an advanced stage and their tumours are usually of the squamous cell type (El-Boulkany *et al.*, 1972; Ghoneim *et al.*, 1972).

Radical cystectomy with urinary diversion appears to offer the best prospect for cure in most cases. We report our experience with 126 patients treated by radical surgery and followed up for a minimum of 10 years.

Patients and Methods

Between 1969 and 1973, 160 patients with clinically resectable bladder tumours were admitted to our department. The different lines of treatment adopted for their management are outlined in Table 1. One-stage radical cystectomy and urinary diversion were carried out for 126 patients. The age and sex distribution of this group at the start of therapy are given in Table 2. The indications for operation were superficial tumours unsuitable for resection because of their size, and infiltrating tumours unsuitable for segmental resection in view of their size and/or location.

Radical operation involved removal of the bladder with its perivesical fat, peritoneal covering, the prostate and the seminal vesicles, together with the distal common iliac, internal iliac and external iliac lymph nodes. In the female, the bladder, urethra, uterus and upper two-thirds of the vagina with the pelvic cellular tissue and the aforementioned lymph nodes were removed (Ghoneim *et al.*, 1972).

Table 1 Treatment of Bladder Cancer Patients 1969-1973

Radical cystectomy	126
Partial cystectomy	14
Simple cystectomy	2
Exploration only	5
Others	13
Total	160

Table 2 Age and Sex Distribution

	Age in years					
	20–	*30–*	*40–*	*50–*	*60+*	*Total*
Males	1	19	68	24	6	118
Females	6	13	19	4	0	42
Total	7	32	87	28	6	160

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Table 3 Methods of Urinary Diversion Following Radical Cystectomy

Type of diversion	*No.*	(%)
Rectal bladder	75	59.50
Ureterocutaneous	43	34 50
Ureterocolic	5	3.90
Gersuny-Lowsely	2	1 40
Ileal conduit	1	0.70
Total	126	

The various methods used for urinary diversion are listed in Table 3. A rectal bladder with a terminal left iliac colostomy was most commonly employed. The justification and functional results of this technique have been previously reported (Ghoneim and Ashamallah, 1974).

Survival data were calculated by the direct method. It was assumed that untraced patients were all dead (minimum survival rate).

Results

Seventeen patients died in hospital after surgery, a post-operative mortality rate of 13.5% (Table 4).

The distribution of patients according to clinical and pathological stages is given in Table 5. Most patients presented initially at an advanced stage. Moreover, there was a tendency to under-estimate the pathological extent of the disease, particularly at the T2 stage. Regional lymph nodes were involved in 23 cases, an incidence of 18.5%. Table 6 shows the tumour histology and grade. Squamous cell tumours accounted for 66% of the cases, most of which were well differentiated.

Table 4 Fatal Post-operative Complications

Hepatorenal failure	2
Heart failure	1
Wound dehiscence	1
Septicaemia	9
Faecal fistula	1
Others	3
Total	17 (13.5%)

Table 5 Clinical and Pathological Stage

	P1	*P2*	*P3*	*P4*
T1	—	—	2	—
T2	1	6	13	1
T3	1	18	67	17
Total	2	24	82	18

Table 6 Tumour Histology and Grade

Histology	*Grade*		*Total*	(%)
	Low	*High*		
Squamous	45	38	83	65.9
Transitional	7	27	34	27
Adenocarcinoma	2	5	7	5.5
Undifferentiated	—	2	2	1 6
Total	54	72	126	100

Table 7 Results of Treatment

Total number exposed to risk	126
Died post-operatively	17
Died from disease	37
Died cause unknown	38
Lost to follow-up	5
Alive and disease-free for more than 10 years	29
% of minimum 10-year survival	23

Details of survival are outlined in Table 7. The 5-year direct survival rate was 32.6% (standard error 4%, $P=0.05$). The 10-year direct survival rate was 23% (standard error 3.7, $P=0.05$). These figures represent minimal direct survival and are uncorrected. The actuarial appraisal of the same data is illustrated in the Figure. Survival was correlated with the various pathological features of the tumour (Tables 8, 9, and 10).

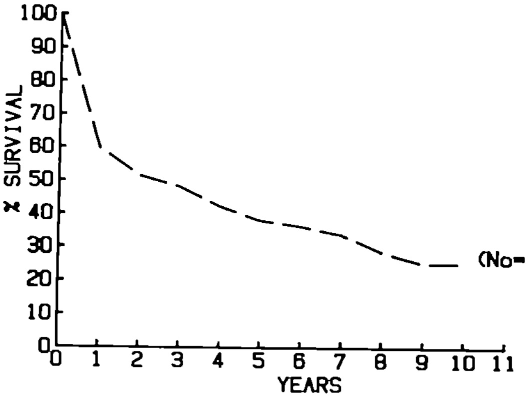

Fig. Survival data for radical cystectomy.

Table 11 delineates the frequency distribution of causes of treatment failures (recurrences or metastasis) relative to their time of onset. Most of the recurrences were local, in the pelvis, and developed within 24 months after initiation of treatment.

Table 8 Survival Relative to Tumour Histology

	Squamous	*Transitional*
Survival proportion	20/83	9/34
Direct 10-year survival %	24	26

Table 9 Survival Relative to Pathological Stage

	Superficial	*Deep*
Survival proportion	5/22	24/104
Direct 10-year survival %	22.7	23

Table 10 Survival Relative to Tumour Grade

	Low	*High*
Survival proportion	18/54	11/72
Direct 10-year survival %	33.3	15.3

Table 11 Failure of Treatment

Year	*Failure of treatment*	*Died cause unknown*	*Total*
0-1	29	4	33
1-2	8	2	10
2-3	1	3	4
3-4	7	0	7
4-4	2	3	5
5+	1	15	16

Discussion

Few reports give 10-year survival figures following cystectomy for cancer. We believe this is the first report dealing with such data for carcinoma of the bilharzial bladder. This is of particular value, since this type of cancer is commonly encountered among relatively young patients. The peak age incidence was reported as 46.3 years by El-Boulkany *et al.* (1972).

A post-operative mortality rate of 13.5% is considered high by today's standards. Our current figures are below 5%. This improvement can be attributed to better technical experience and significant improvement in dealing with infective complications, which were the main cause of post-operative fatalities.

Analysis of treatment failures indicates that most developed within 24 months after initiation of treatment and were largely due to local recurrence rather than distant metastases.

The gradual decline in the actuarial survival curve after 5 years presumably reflected attrition from natural causes rather than deaths from cancer. Evidence of late death from cancer (after 5 years) was found in only one patient.

Analysis of survival figures relative to the various pathological features of the tumour revealed that squamous and transitional tumours have a similar prognosis, a finding which was also reported in non-bilharzial bladder tumours by Richie *et al.* (1976). It was also seen that tumour grade is the most critical prognostic index.

All of these observations point to the need for improvement in the results for this type of cancer; adjuvant treatment directed to the pelvis rather than systemic chemotherapy might be necessary. Pre-operative radiotherapy enhanced by the use of a hypoxic cell sensitiser may be a logical approach. Furthermore, since patients who do not develop metastases or recurrence for 2 years have a significant chance of prolonged disease-free survival, more attention must be given to their complete rehabilitation. This is of particular importance among males in whom normal sexual life can be resumed following a penile implant.

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The Authors

M. A. Ghoneim, MD, Professor of Urology and Director of Urology and Nephrology Centre

A Ashamalla, MD, Professor of Urology.

M. A. Gaballa, MD, Assistant Professor of Urology

E. I. Ibrahim, MD, Lecturer in Urology.

Requests for reprints to: M A. Ghoneim, Urology and Nephrology Centre, Mansoura University, Mansoura, Egypt.

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Evaluation of the Efficacy of Oral Methotrexate in the Prevention of Recurrence of Superficial Bladder Tumours

J. L. NOGUEIRA MARCH, A. OJEA, L. FIGUEIREDO, D. JAMARDO, E. DIEZ and
J. PEREZ VILLANUEVA

Department of Urology, Vigo General Hospital, Vigo, Spain

Summary—Twenty-four patients with previously untreated T1 transitional cell carcinoma of the bladder were treated with oral methotrexate 50 mg weekly for 18 months. Thirteen developed tumour recurrences (recurrence index 11 per 100 patient months at risk) and in one-third of the patients treatment was stopped because of unwanted side effects. These results are no better than our previous experience with intravesical Adriamycin, thiotepa or cisplatin.

Superficial bladder tumours that are not amenable to transurethral resection are now exceptional and it is generally accepted that complementary chemotherapy is needed for prophylaxis against tumour recurrence.

Conventional intravesical chemotherapy requiring repeated catheterisation is inconvenient and uncomfortable and the incidence of chemical cystitis is far from negligible. The possibility of administering by mouth a cytostatic agent that is excreted in the urine and is active against the urothelium would obviate these disadvantages.

Methotrexate is a suitable agent since it is absorbed from the stomach in low dosage and, although partially metabolised by the liver, is mainly excreted unaltered in the urine. Previous studies have suggested that 50 mg of oral methotrexate may reach cytotoxic levels in plasma and urine for longer periods of time than can be achieved by intravesical instillation (Hall *et al.*, 1974; Turner *et al.*, 1977). We report the results of a study of oral methotrexate following the work of Hall *et al.* (1981).

Patients and Methods

Twenty-four patients with previously untreated transitional cell carcinoma of the bladder, UICC category T1, have been studied; 4% of the tumours were well differentiated, 83% moderately differentiated and 13% poorly differentiated; 42% of the patients had 3 or more tumours when first examined.

Treatment comprised 50 mg methotrexate as syrup administered weekly commencing 1 week after complete transurethral resection. Treatment was suspended if the platelets fell below 75,000 to 100,000/mm^3 or the granulocytes below 1500 to 2000/mm^3 or if patients developed mucositis, erythema, neurological side effects or nausea and vomiting that could not be controlled with conventional anti-emetics. Blood counts were repeated weekly; urine cytology and cystoscopy were repeated at 3-monthly intervals unless the first two examinations were normal, in which case cystoscopy was performed 6-monthly.

Results

Thirteen of the 24 patients developed recurrent tumours (54%), an overall recurrence rate of 11 recurrences per 100 patient months at risk (Table 1). The incidence of recurrence was related to tumour grade but not to tumour multiplicity (Table 2). The tumour category of recurrences was

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Table 1 Results of Prophylactic Oral Methotrexate

Number of patients treated	24
Number of patients developing recurrent tumours	13 (54%)
Total number of tumour recurrences	19
Total number of months of follow-up	171
Number of recurrences per 100 patient months at risk	11.1

Table 2 Incidence of Tumour Recurrence vs Tumour Grade and Multiplicity at Initial Diagnosis

Tumour grade	*Percentage developing tumour recurrence*
Well differentiated	0
Moderately differentiated	55
Poorly differentiated	67
Tumour multiplicity	
Patients with less than 3 tumours	50
Patients with more than 3 tumours	60

the same as the initial tumour in 92% of patients and lower in 8%. The degree of differentiation and the multiplicity of tumours also remained unchanged in most patients (Table 3).

Table 3 Changes in Tumour Stage, Grade and Multiplicity Following Prophylactic Oral Methotrexate

	No change	*Increase*	*Decrease*
Stage	92%	0	8%
Grade	84%	8%	8%
Multiplicity	61%	31%	8%

Toxicity was considerable. Vomiting, diarrhoea, oral ulceration and thrombocytopenia occurred in 10 patients (32%). In 7 of these patients mucositis and gastro-intestinal symptoms necessitated suspension of treatment before the first review cystoscopy and these patients were excluded from subsequent analysis. The other 3 patients developed thrombocytopenia and treatment had to be stopped after 18, 24 and 35 doses of methotrexate.

Discussion

Our results with oral methotrexate were not very satisfactory as the incidence of tumour recurrence in the small group of patients treated was greater than that observed in similar patients treated previously in our department with thiotepa, Adriamycin or cisplatin (Nogueira March *et al.*, 1984; Ojea *et al.*, 1984) (Fig.). Furthermore, methotrexate caused significant toxicity, necessitating the suspension of treatment in one-third of the patients.

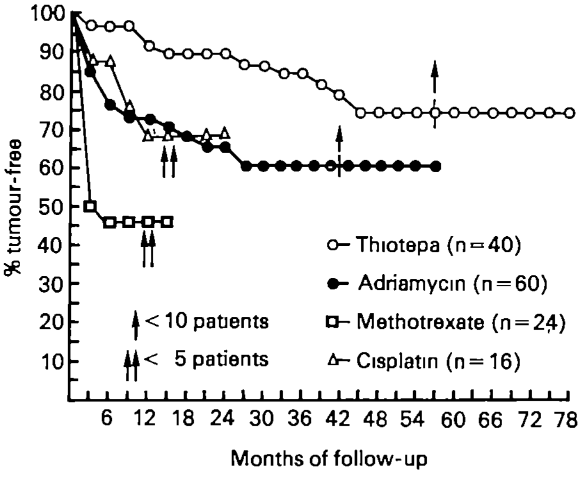

Fig. Tumour recurrence following prophylactic oral methotrexate (present study) compared with intravesical thiotepa, Adriamycin and cisplatin (previous, non-randomised study)

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The Authors

J. L. Nogueira March, MD, Chief, Urology Service.
L. Figueiredo, MD, Registrar in Urology.
A. Ojea, MD, House Officer.
D. Jamardo, MD, House Officer.
E. Diez, MD, Resident in Urology.
J Perez Villanueva, MD, Chief, Pathology Service.

Requests for reprints to: J. L. Nogueira March, Department of Urology, Vigo General Hospital, Vigo, Spain.

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Bladder Neck Contracture Following Prostatectomy

Z. SIKAFI, M. R. BUTLER, V. LANE, J. D. O'FLYNN and J. M. FITZPATRICK

Department of Urology, Meath Hospital, Dublin

Summary—In an 11-year period, 49 patients developed bladder neck contracture after prostatectomy—an incidence of 0.86%. This complication was found to be more common after resection of small fibrous hyperplastic prostates. The best results for treatment of the contracture were obtained after bladder neck incision, which gave a 9% incidence of recurrence; after transurethral resection of the bladder neck contracture the recurrence rate was 46%, and after bladder neck dilatation it rose to 100%.

Post-operative bladder neck contracture is an uncommon but disappointing complication of prostatectomy. It is reported to occur more frequently after transurethral resection of prostate (TURP). The degree of contracture depends on the extent of tissue damage caused by electro-resection at the bladder neck. In its mildest form the contracture produces an elevation of the posterior lip of the vesical neck or slight circumferential narrowing and rigidity. The severest form is characterised by formation of a diaphragm which occludes the whole vesical neck down to a pinhole opening placed centrally (Greene and Robinson, 1965).

Patients and Methods

From January 1973 to December 1983 inclusive, 51 patients with post-operative contracture of the bladder neck were seen at the Urological Department of the Meath Hospital. The total number of prostatectomies done in that period was 5697. Forty-one patients had a transurethral resection of the prostate, seven patients had a retropubic prostatectomy and one a transvesical prostatectomy. Two further patients were excluded from the study: one developed interstitial cystitis with bladder contraction and subsequently had a urinary diversion, while the other developed an atonic bladder which required intermittent self-catheterisation.

The patients' ages ranged from 54 to 84 years (average 71). The weight of prostatic tissue from patients who had undergone TURP ranged from 2 to 50 g (average 10.2) (Fig). The interval between

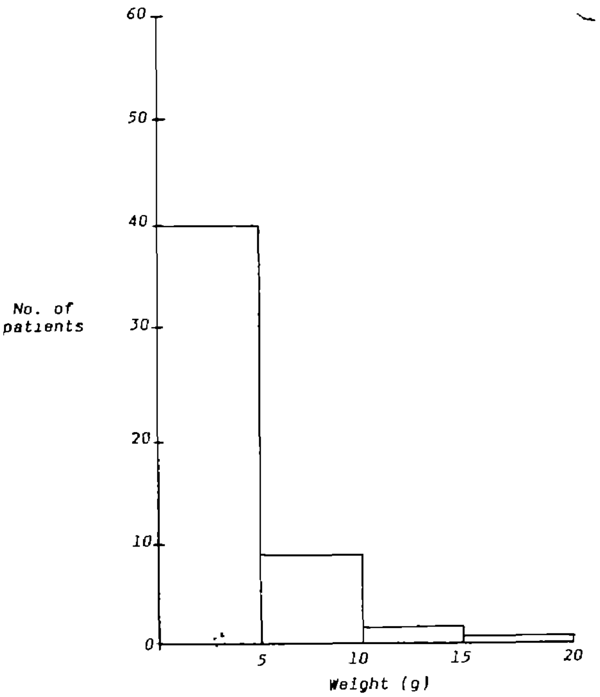

Fig. Weight of prostates at time of original resection.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984.

prostatectomy and presentation with symptoms of bladder neck contracture ranged from 2 months to 10 years. The presenting symptoms in 35 patients were frequency, nocturia and a poor stream. Eight presented with acute urinary retention and six had symptoms of incontinence due to chronic retention with overflow (Table 1).

Table 1 Symptoms of Patients with Bladder Neck Contracture

Presenting symptoms	*No of patients*
Frequency, nocturia and poor stream	35 (72%)
Acute retention	8 (16%)
Incontinence of urine	6 (12%)

All patients were diagnosed by cystourethroscopy. Only 10 were found to have the severest form of contracture with pinhole narrowing of the bladder neck.

The treatment of all patients can be divided into three groups (Table 2). Twenty-one of the 49 patients were treated by bladder neck incision (BNI) with an ACMI knife electrode or a cold knife using a Sachse optical urethrotome. The incision extended from the bladder neck to the verumontanum and penetrated deeply into the prostatic capsule to expose periprostatic fat. Nineteen patients had two or more incisions into the capsule at the bladder neck, with only two patients having had a single bladder neck incision at the time of the primary operative management of their contracture. The bladder neck contractures in 26 of the 49 patients were treated by hot loop electro-resection confined to the bladder neck only.

Table 2 Post-prostatectomy Bladder Neck Contracture: Results of Treatment

Operation	*No. of patients*	*No of patients symptom-free*
Bladder neck incision	21	19 (91%)
TUR of bladder neck	26	14 (54%)
Urethral dilatation	2	0

Results

The results of treatment are shown in Tables 2 and 3. Two of the 21 patients treated by bladder neck incision required repeat procedures because of recurrence of contracture. One of these patients needed one further bladder neck incision for cure and the second patient required three bladder neck incisions for cure. The recurrence rate of bladder neck contracture after bladder neck incision was 9.2%. Of the 26 patients treated by transurethral resection of the bladder neck 12 needed repeat procedures due to recurrence of their bladder neck contracture. Five patients in this group required three further bladder neck resections for success and one patient underwent bladder neck resection on six occasions before obtaining relief by a Y-V plasty at the bladder neck (Table 3). The two patients who were treated initially by urethral dilatation failed to respond and were subsequently dealt with by bladder neck incision.

Table 3 Results in 14 Patients with Bladder Neck Contracture not Cured by the Primary Operative Treatment

Primary operative treatment	*Secondary operative treatment*
Bladder neck incision (2 patients)	One further bladder neck incision (1 patient) Three further bladder neck incisions (1 patient)
TUR bladder neck (12 patients)	Two further TUR bladder neck (6 patients) Three further TUR bladder neck (5 patients) Six further TUR bladder neck (1 patient)

Discussion

Robinson and Greene (1962) demonstrated experimentally in dogs that trauma limited to the vesical neck results in contracture. Extensive electroresection to this area is an important factor in the aetiology of post-prostatectomy bladder neck fibrosis. Bladder neck contractures are less likely to occur when the prostate is large, or where the prostate extends intravesically. Apparently in these circumstances the vesical neck is pushed aside and is protected (Greene and Robinson, 1965).

The onset of symptoms due to bladder neck contracture varies from a few weeks after prostatectomy to as long as 10 years. Greene and Leary (1967) showed that diaphragmatic contractures can form as early as 23 days after resection.

To avoid this complication Uhle and Kohler (1969) suggested that in small prostates the bladder neck should not be resected radically but, if this is necessary, the coagulation of tissue in this area should be kept to a minimum.

The incidence of bladder neck contracture after retropubic and transvesical prostatectomy is less than after transurethral electro-resection. There are a number of factors involved but electro-resection appears to cause more damage to this area than that caused by open surgery. Millin (1947) reported five bladder neck contractures in his first 75 consecutive patients. Bu excising a wedge from the posterior lip of the bladder and fixing the mucosa across the bladder neck he eliminated this complication in the next 200 consecutive cases.

The diagnosis is usually made either by cystourethroscopy or retrograde urethrography in which the characteristic "tooth-paste" sign may occur. The development of urodynamic studies in combination with videocystography has defined accurately the true nature of the disorder of the bladder neck (Turner-Warwick *et al.*, 1973).

Approaches to treatment have varied. Greene and Robinson (1966) advocated dilatation of the contracture followed by electro-resection of the fibrous tissue. They claimed that injection of the area of the vesical neck with cortisone derivatives as an adjuvant to treatment was beneficial. Uhle and Kohler (1969) used open revision of the vesical neck by circumferential excision of the fibrous tissue with a scalpel or scissors in all cases in which the contracture was diaphragmatic in nature. Keitzer *et al.* (1969) cured 75% of their patients by bilateral bladder neck incision. Their incision extended from the bladder neck to the verumontanum and deeply into the prostatic capsule. Moisey *et al.* (1982) obtained good subjective and urodynamic results in their series of bladder neck contractures after unilateral bladder neck incisions. This series closely parallels the experience of others. The most notable feature was the relatively small size of the prostate resected. In addition, poor results were obtained when the bladder neck contracture was treated by re-resection of the bladder with a hot loop. The best results were obtained by bladder neck incision using either a hot knife or a Sachse urethrotome.

It is concluded that bladder neck contracture after transurethral resection of the prostate is best treated by bladder neck incision. Repeat resection of the contracture at the bladder neck by hot loop electrodiathermy gives poor results and is not recommended.

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The Authors

Z. Sikafi, FRCSI, Registrar in Urology.
M. R. Butler, FRCS, FRCSI, Consultant Urologist.
V Lane, MCh, FRCSI, Consultant Urologist.
J. D. O'Flynn, MCh, FRCSI, Consultant Urologist.
J. M. Fitzpatrick, MCh, FRCSI, Consultant Urologist.

Requests for reprints to. J. M. Fitzpatrick, Department of Urology, Meath Hospital, Dublin 8, Ireland.

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Blood Loss Measurement during Transurethral Resection of the Prostate Gland

M. FREEDMAN, S. W. VAN DER MOLEN and E. MAKINGS

Departments of Anaesthesia and Urology, University of the Witwatersrand, Johannesburg Hospital, Johannesburg, Republic of South Africa

Summary—The application of the indicator dilution technique for the estimation of blood loss during transurethral resection of the prostate gland is explained. The feasibility of using potassium ions as an intrinsic indicator was investigated. The most important factors affecting blood loss are considered. The advantages and inherent sources of error are discussed and some tentative conclusions drawn concerning the factors affecting blood loss.

Blood loss during transurethral resection should, if possible, be continuously and accurately measured. Previous studies have relied upon photocolorimetric and photoelectric measurements of the fluid drained and collected during the operation. The readings obtained were then compared with a calibration curve prepared with known haemoglobin concentrations, related either to the optical density given by a colorimeter or to the electrolyte conductivity of a standard dilution. These methods have not been routinely adopted because of the lack of a suitable control and the fact that the necessary equipment is not readily available at all institutions performing transurethral surgery (Litin and Emett, 1959; Mainland, 1966; Desmond, 1973; Hansen *et al.*, 1978).

Blood loss during transurethral resection cannot be estimated by serial weighing of the patient because of absorption of irrigation fluid and administration of intravenous fluids intra-operatively. Serial measurements of blood haemoglobin concentration and of haematocrit are meaningless during acute blood loss (Murray and Potts, 1960).

The mainstay of assessing the deficit in a patient is to monitor the physiological responses to that deficit, principally by haemodynamic measurements. These responses are, however, easily confounded by influences other than blood loss during anaesthesia and surgery, and there are circumstances in which a deficit large enough to elicit a response is also large enough to constitute a serious haemodynamic compromise. During transurethral resection, however, it is possible to collect nearly all of the blood lost with the effluent collected during the resection. The blood lost (X ml) may be estimated by application of the indicator dilution principle. If [Id] is the concentration of an indicator substance (I) in the collected effluent, and [Io] is the original concentration in the patient's blood which was lost, provided that the volume of irrigation fluid (Y ml) is known, the volume of blood which was lost (X ml) may be calculated as follows:

$$X \, . \, [Io] = (X + Y) \, . \, [Id]$$

from which

$$X = \frac{Y \, . \, [Id]}{[Io] - [Id]} \qquad (1)$$

This equation, or variants of it, is common to all dilutional approaches, although the indicator may be varied. The accuracy of each approach depends upon the accuracy with which the chosen indicator can be measured and the degree to which contamination by additional amounts of indicator is avoided. Unless serial measurements are also made of the concentration [Io] in the blood which is lost, the assumption is made that [Io] remains at a

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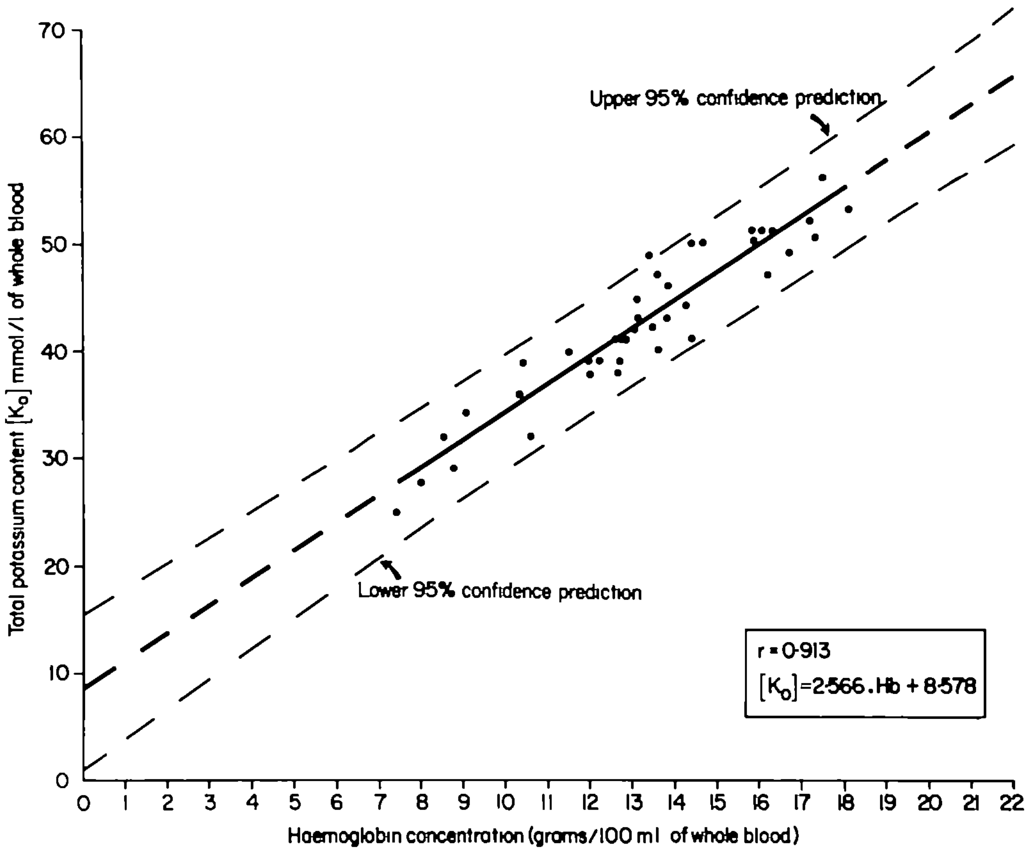

Fig. 1 Relationship between the total potassium content (mmol/l) and the haemoglobin concentration (g/100 ml) of whole blood. ----, upper and lower 95% confidence limits

constant value which is commonly taken to be that measured pre-operatively.

This report describes preliminary investigations into the feasibility of using potassium as an intrinsic indicator. For this purpose the appropriate version of equation (1) would be:

$$X = \frac{Y.[Kd]}{[Ko] - [Kd]} \qquad (2)$$

where [Kd] is the potassium concentration in mmol/l of the effluent, measured by flame photometry. The total potassium content per litre of whole blood [Ko] is equal to that contained within the cellular elements [Kc] plus that contained within the plasma [Kp], from which

$$[Ko] = [Kc] + (1 - \text{haematocrit}).[Kp]$$

The total potassium content per litre of whole blood may, however, be estimated indirectly from a previously determined relationship between the cellular potassium content/litre and the haemoglobin concentration of whole blood (Freedman, 1984).

If (Hb_0) is the haemoglobin concentration (g/100 ml), the total potassium content/litre of that blood maybe estimated as:

$$[Ko] = m_1.(Hb_0) + c_1$$

(where $m_1 = 2.566$ and $c_1 = 8.578$).

Since the plasma potassium content is only about one twentieth that of the red cells, a more complex equation which takes into account the effects of haematocrit and plasma potassium [Kp] does not improve the accuracy of the estimate significantly.

Blood loss may then be calculated and estimated as:

$$X = \frac{Y.[Kd]}{m_1.(Hb_0) + c_1 - [Kd]} \qquad (3)$$

This is expressed as a nomogram in Figure 2.

Methods

Blood loss was estimated during 43 transurethral

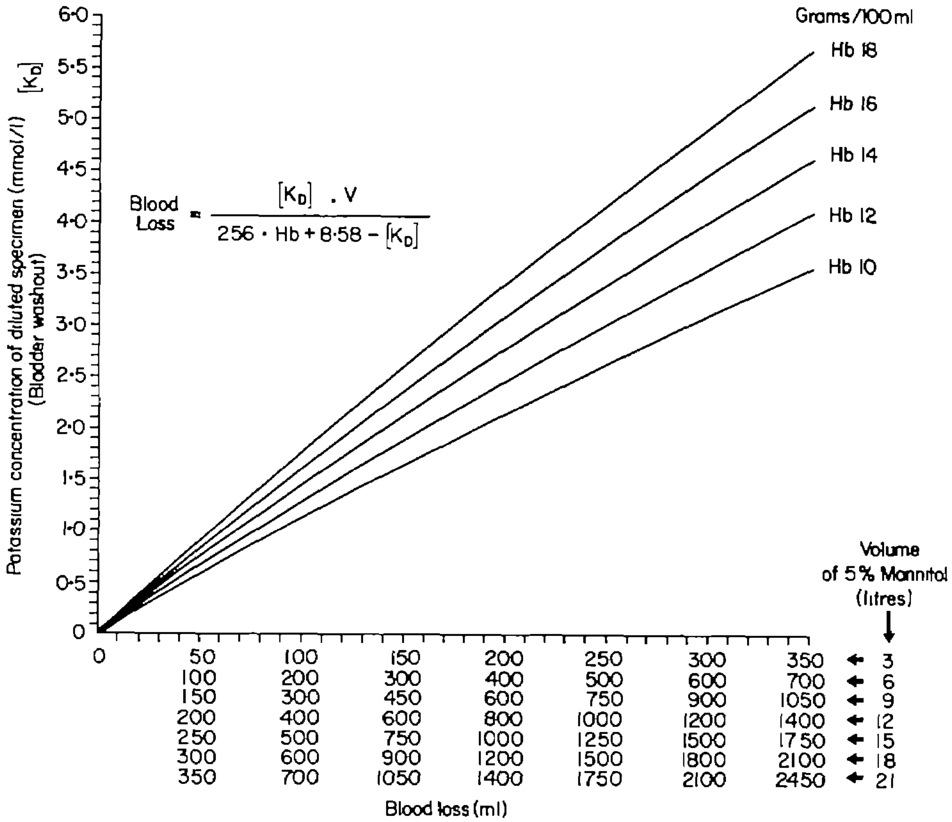

Fig. 2 Nomogram for estimating the volume of blood lost during transurethral resections, from the potassium concentration [Kd] of the effluent collected during the resection (mmol/l) and the haemoglobin concentration of a patient's blood (g/100 ml).

resections of the prostate over a 4-month period. Three surgeons were included in the study: two were consultant urologists who performed 25 and 5 resections respectively, and the third a registrar in his second year of training who performed 13 resections. The anaesthetics were administered by 15 anaesthetists over this period. There was no influence or limitation as to who should perform the surgery or as to the anaesthetic technique. Twenty-five spinal, 7 epidural and 11 general anaesthetics were administered.

All estimates were performed according to the following rigid protocol. Each patient's age, haemoglobin concentration and plasma potassium concentration were noted pre-operatively. Each patient's bladder was emptied of urine before starting the collection of effluent into a totally closed collection system. Mannitol 5% was used as the irrigation fluid in all cases.

An estimate of blood loss was made for each patient 15 min after the start of resection as well as at the end of the procedure.

To make an estimate, the effluent was stirred well and exactly 5 ml were then removed and haemolysed by adding 5 drops of a high speed stromatolysing agent "Zap-O-Globin" (30% potassium cyanide). The volume of irrigation fluid used at that time was noted. The potassium concentration of the haemolysed sample was then analysed by flame photometry (I.L -343- Digital Flame Photometry), and 0.7 mmol/l, which was the contribution from the potassium cyanide, was subtracted before reading off the volume of blood lost on the nomogram.

The total time taken for resection, the mass of tissue resected, the surgeon's estimate of blood loss and any comments of the anaesthetist were noted.

Results

The patients ranged in age from 52 to 91 years. The total loss ranged from 90 to 2080 ml (mean 605 ml). Although the mean loss under general anaesthesia (775 ml) was greater than that for spinal (561 ml) and epidural anaesthesia (527 ml), this difference was not statistically significant. There was no significant difference in total loss whether the operation was performed by the consultants or the registrar, but only in resections performed by the registrar was the total loss related to the time taken for resection (r = 0.7559, n = 13).

There was a correlation between the total loss and the mass of tissue resected (r = 0.6594, n = 43).

The time taken for resection ranged from 30 to 120 min (mean 75 min). Although the consultants were faster (62 and 75 min respectively) than the registrar (82 min), the difference was not statistically significant. Only for the consultants was there a correlation of time taken for resection with mass of tissue resected (r = 0.9785, n = 5) and (r = 0.5526, n = 25) respectively.

The mean time for resection under epidural anaesthesia (67.5 min) was shorter than that for spinal (75.7 min), which was in turn shorter than that for general anaesthesia (80 min) but this difference was not statistically significant.

The rate of loss decreased with longer resection times (Fig. 3) and the total loss/mass of tissue resected decreased with larger glands (Fig. 4).

The loss at 15 min correlated well with the total loss (r = 0.5592, n = 43) and was not influenced by

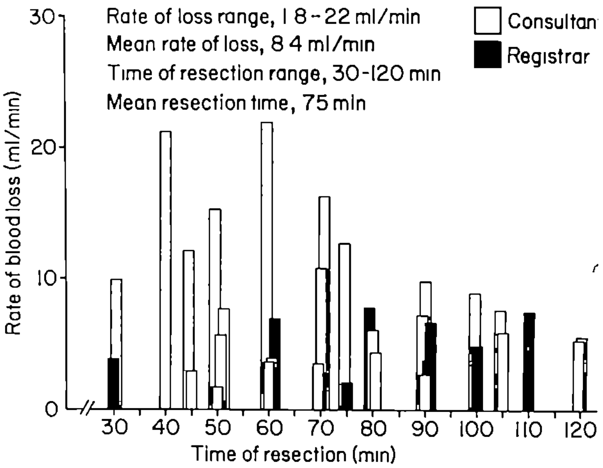

Fig. 3 Relationship between the rate of blood loss (ml/min) and the resection time (min) during transurethral resection of the prostate.

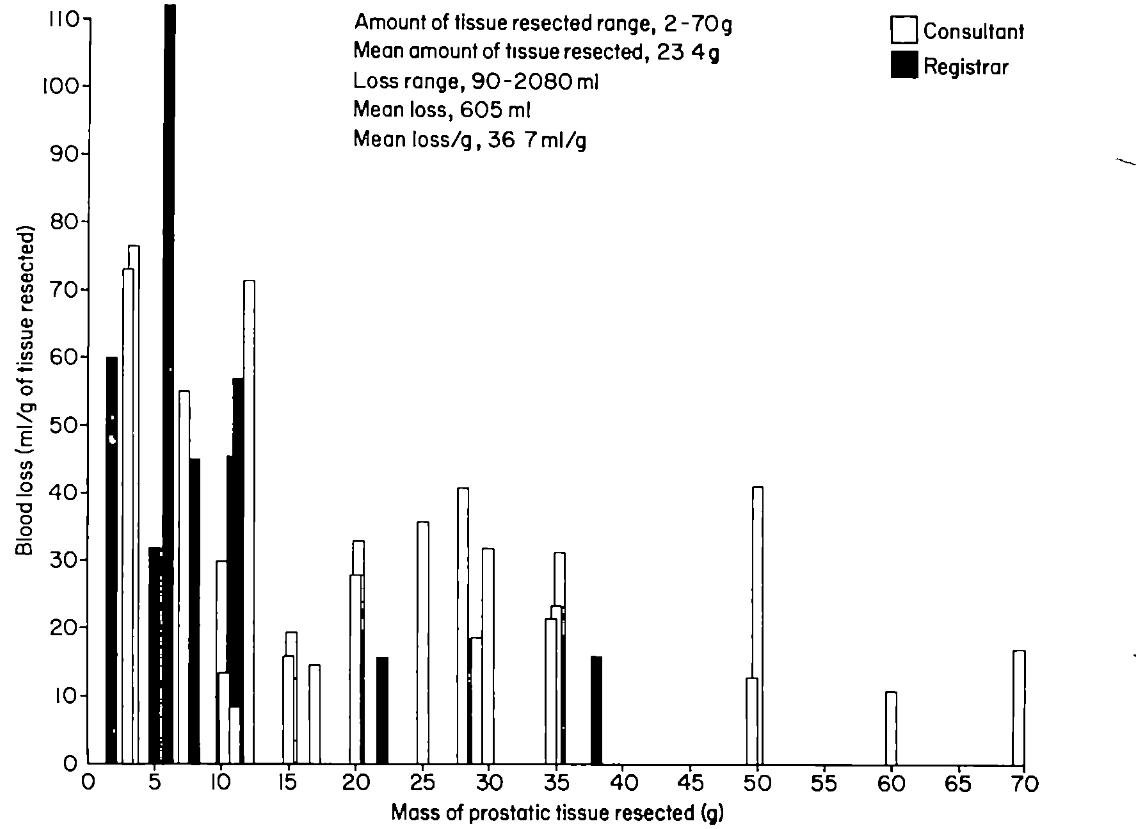

Fig. 4 Relationship between blood loss (ml/g) and the mass of prostatic tissue resected (g).

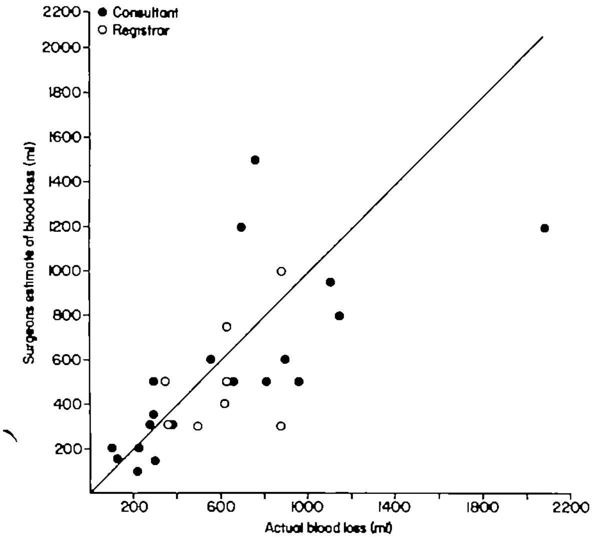

Fig. 5 Comparison between the surgeon's estimate of blood loss and the measured blood loss during transurethral prostatic resection.

the choice of anaesthetic or by the surgeon. The mass of tissue resected ranged from 2 to 60 g (mean 23.4 g). The mean rate of loss was 8.4 ml/min and the mean loss/g was 36.7 ml/g. A comparison of the surgeon's estimate with the measured blood loss is shown in Figure 5.

Eleven of the anaesthetists found the procedure helpful and easy to perform.

Discussion

The method is neither new or original, but is an application of the indicator dilution principle. It is a hybrid technique which combines the advantages of using an easily and accurately measured ion, namely potassium, with an old indicator of red cell loss—haemoglobin. The method is quick, reproducible and uses laboratory data and equipment which are generally available.

The disadvantages are that the accuracy hinges upon a derived value for total potassium content/litre of whole blood. This value is not always a true reflection of the actual total potassiun content at the time of loss. Many factors such as rapid infusion of large volumes of crystalloids, massive blood volume replacement, administration of succinylcholine, changes in acid/base status, absorption of irrigation fluid and urinary potassium content add further uncertainty to the estimate (Freedman, 1984).

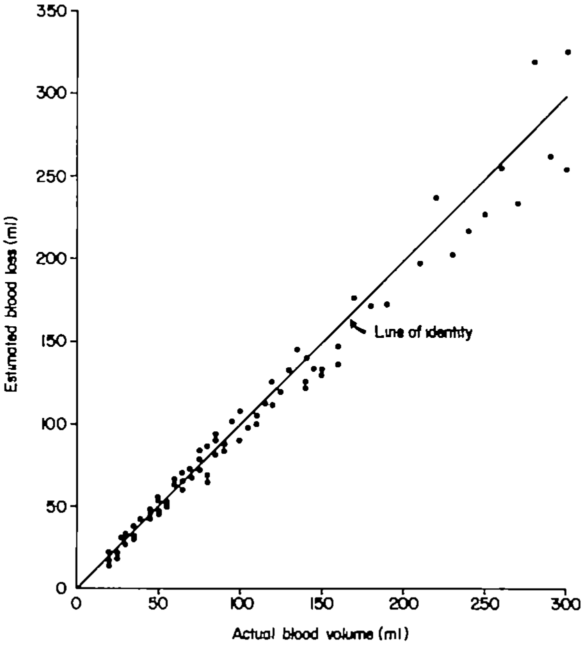

Fig. 6 Comparison between the actual and the estimated volume of blood lost using the blood loss nomogram of Figure 2.

While the method was sufficiently accurate in a controlled laboratory situation (Fig. 6), these findings may not hold true in a clinical situation.

Because of these problems, the actual blood loss values obtained during any resection must be viewed with circumspection and should always be correlated with the clinical condition of the patient. Nevertheless, most anaesthetists found the estimates to be helpful and our surgeons became more aware of blood loss during the procedure.

The number of cases in this series is too small for definite conclusions to be drawn. The findings do, however, suggest that there is a greater volume of blood lost when resection is performed under general anaesthesia compared with regional anaesthesia. Greater loss occurred with larger amounts of prostatic tissue resected, but the rate of loss decreased with time and the loss/g decreased with larger glands. This may be due to haemostasis occurring spontaneously during the resections.

With larger glands the cutting speed is initially higher and the size of the cut pieces larger during the first part of the resection, the surgeons being more meticulous during larger and longer resections as they approach the capsule. Smaller glands may also be expected to have a relatively greater surface area/mass ratio compared with larger glands, which may partly account for the relatively greater bleeding.

Each estimate is easy to perform and provides a means of comparing the factors which may influence blood loss.

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The Authors

M. Freedman, MB, BCh, DA(SA), FFA(SA), Senior Registrar, Department of Anaesthesia.

S. W. van der Molen, MD, Senior Consultant Urologist

E. Makings, MSc(Dent), DipMicrobiol, DipLabAniSci, Principal Technician, Department of Anaesthesia.

Requests for reprints to: M. Freedman, 3 Luderitz Street, P.O. Box 513, Wendywood 2144, Republic of South Africa

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Bone Imaging and Serum Phosphatases in Prostatic Carcinoma

M. C. BISHOP, J. G. HARDY, M. C. TAYLOR, M. L. WASTIE and R. J. LEMBERGER

Department of Urology, City Hospital, Nottingham

Summary—One hundred and twenty-seven patients with locally advanced prostatic cancer were evaluated for the presence and progress of bone metastases before and during hormonal therapy, by serial radionuclide imaging and frequent measurement of plasma acid (tartrate-labile) and alkaline phosphatase. For comparison, serial changes in imaging and phosphatases were classified in each patient into one of six groups.

Of 71 patients with negative imaging before treatment, 82% had normal alkaline phosphatase levels and 83% had normal acid phosphatase levels. Of 56 patients with bone metastases at presentation, false negative alkaline and acid phosphatase levels were noted in 18% and 36% respectively, though a few patients eventually developed abnormal levels.

Serial plasma biochemistry and particularly alkaline phosphatase showed a response to treatment which was not always obvious on imaging. An assessment of the hepatic component of alkaline phosphatase by reference to plasma gamma glutamyl transpeptidase and isoenzyme electrophoresis was helpful in the evaluation of a false positive result but unnecessary where imaging was positive and phosphatase elevated.

It is concluded that serial alkaline phosphatase estimation is essential in the follow-up of patients with prostatic cancer and bone metastases, and probably renders serial imaging studies superfluous once the presence of skeletal metastases has been proven. By comparison, acid phosphatase is a much less effective marker.

Agreement has yet to be reached on the management of most forms of prostatic cancer. Whatever treatment policy is operative, identification of patients with metastases at presentation is important. The assessment of lymph node involvement is unsatisfactory (Chisholm, 1982) and most urologists regard radionuclide bone imaging as the single most effective screening investigation (O'Donoghue *et al.*, 1978; Hardy *et al.*, 1980). Most metastases appear as discrete areas of increased uptake of the radiopharmaceutical agent. The method is much more sensitive than skeletal X-rays (Fitzpatrick *et al.*, 1978), though these are often required to distinguish a number of benign conditions such as Paget's disease, osteo-arthrosis and fractures, which can give similar images. Serial bone imaging is also widely used as a marker of tumour activity in response to treatment (Fitzpatrick *et al.*, 1978; Perkins *et al.*, 1982). However, there are drawbacks: changes in uptake of the tracer in different parts of the skeleton can be inconsistent and complicate overall assessment of treatment response. Also, the method is time-consuming and expensive if very frequent monitoring is contemplated and a plasma biochemical measurement may be simpler and more appropriate.

Plasma acid phosphatase, a lyosomal enzyme derived from prostatic acinar cells, is often elevated in patients with locally advanced or metastatic disease. Many other tissues produce this enzyme but its specificity can be improved by tartrate inhibition and in the modern immunoassay techniques (Goldenberg *et al.*, 1982; Vihko *et al.*, 1982; Pontes, 1983). Since the pioneering work of Gutman *et al.*

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(1936), urologists have always considered acid phosphatase an aid to diagnosis, staging and prognosis in prostatic cancer.

Plasma alkaline phosphatase is highly regarded in the diagnosis and follow-up of a number of metabolic diseases. However, despite early recognition of its potential in prostatic cancer (Gutman *et al.*, 1936; Huggins and Hodges, 1941), it has been relatively neglected as a marker of bone metastases; yet these are commonly sclerotic, with a preponderance of osteoblastic activity which will be expected to give elevated plasma levels.

In this study plasma acid and alkaline phosphatase have been carefully reassessed in comparison with serial radionuclide bone imaging in the diagnosis and follow-up of bone metastases.

Patients and Methods

One hundred and forty-four patients with advanced prostatic carcinoma (T3/4) were entered into a trial of estramustine phosphate (Estracyt 280 mg bd) against conventional hormonal therapy (diethyl stilboestrol 1 mg tds) as primary treatment. Patients were aged from 56 to 86 years at presentation. The protocol included regular evaluation for the development and progression of bone metastases by skeletal scintigraphy, radiography and measurement of plasma alkaline and acid phosphatase. Data from 127 patients were regarded as adequate for analysis.

Each patient was imaged 3 h after an intravenous dose of 400 MBq ^{99m}Tc-labelled methylene diphosphonate. The spine, ribs, sternum, pelvis and upper femora were examined and the data recorded by computer for quantification (Hardy *et al.*, 1980). The method related bone uptake to an external reference standard. A site of increased radiopharmaceutical uptake was considered to be due to metastatic bone disease if the patient had normal radiographs or no radiographic evidence of diseases other than metastases to account for the abnormality.

The mean period of follow-up between the initial and final bone imaging was 24 months (range 3-72). Initially, serial imaging was undertaken at 3-monthly intervals, but for patients whose images did not change the intervals were lengthened. The mean period between imaging was 5 months and each patient underwent an average of 4.7 studies. The plasma phosphatases were measured more frequently, initially at 2-weekly intervals, then monthly and thereafter every 3 months. The enzyme assays were performed by standard laboratory techniques. The tartrate labile prostatic fraction of acid phosphatase was measured in every case. The hepatic contribution to elevation of plasma alkaline phosphatase was assessed by estimation of gamma glutamyl transpeptidase (gamma GT) and starch gel electrophoresis.

On the basis of serial bone images the patients were divided into six groups (Table 1). Corresponding groups were devised based on the changes in phosphatase levels (Fig. 1). Metastatic bone lesions were considered to be resolving if they decreased in size or exhibited reduction in uptake of the radiopharmaceutical. Progression was defined by the appearance of a new metastatic site or an increase in size of a previously detected lesion even if other sites appeared to be resolving.

Table 1 Classification of Serial Radionuclide Bone Imaging

Group	*Imaging*
1	Normal
2	Initially normal, metastases developing
3	Metastases at presentation, subsequent improvement
4	Metastases at presentation; improvement then deterioration
5	Metastases showing no change
6	Metastases showing deterioration

A biochemical response with matching clinical improvement could be identified from a fall in the phosphatase levels but this was sometimes preceded by a swift and dramatic rise in the plasma alkaline phosphatase level (Fig. 1). This "flare" occurred soon after the start of treatment and was followed by a fall towards normal limits. This could either be maintained (group 3) or be followed by a secondary elevation possibly indicating hormone "escape" (group 4). For the purposes of a simple comparison between plasma alkaline phosphatase and extent of metastases, the bone images were classified as follows, according to the number of involved sites:

+1 metastatic focus
++2 or 3 discrete foci
+++4 or more discrete foci, or diffuse involvement.

Results

Comparisons between groups summarising serial changes in bone images and biochemical measurements are shown in Table 2.

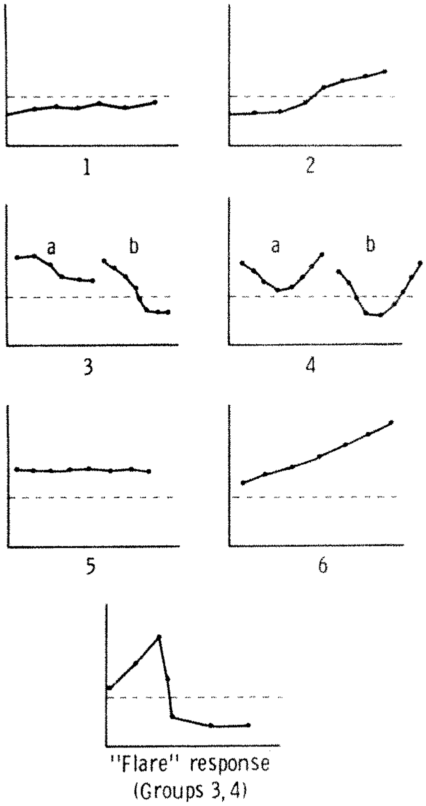

Fig. 1 Classification of serial plasma phosphatases. Group 1: Serial changes within normal limits. Group 2: Initial (pre-treatment) level normal; subsequent (on treatment) levels elevated. Group 3: Initial levels elevated; subsequent fall. (a) minimum level above normal range. (b) minimum level within normal range. Group 4: Initial levels elevated; subsequent fall, then rise. (a) minimum level above normal range. (b) minimum level within normal range. Group 5: Initial level elevated; later no change. Group 6: Initial level elevated; subsequent levels rising.
(Normal ranges: plasma acid phosphatase 0-4 iu/l; alkaline phosphatase 50-190 iu/l).

At Presentation

Initial bone images negative (*groups 1 and 2*) Of 71 patients with negative images at presentation (56% of the total), normal alkaline and acid phosphatase levels were noted in 82 and 83% respectively.

Initial bone images positive (*groups 3-6*) Of 56 patients with positive images at presentation, 10 (18%) and 20 (36%) had false negative alkaline and acid phosphatase levels respectively. Four such patients ultimately showed elevation of alkaline phosphatase and 5 had elevation of acid phosphatase, suggesting that the bone images pre-dated biochemical evidence of bone metastases.

Serial Changes on Treatment

Group 1 Normal serial imaging Of 58 patients whose images remained clear, plasma alkaline phosphatase and acid phosphatase remained within normal limits in 41 (71%) and 46 (79%) respectively. Of the 17 patients with initially, or ultimately false positive alkaline phosphatase levels, 8 had biochemical evidence of liver involvement. In 3 others the rise was pre-terminal, death being due to cardiovascular causes and probably a result of passive liver congestion. In 4 more patients there was reason to suppose that the elevated alkaline phosphatase could have been due to bone metastases. One patient had bone pain, 2 demonstrated the bone isoenzyme on serum electrophoresis and another had typical group 4 changes on treatment (Fig. 1). Two patients remained for whom there was no obvious cause. However, plasma alkaline phosphatase was only slightly elevated and ultimately settled to normal limits. For acid phosphatase, 11 patients had initially elevated levels which fell to normal on

Table 2 Patients Classified According to Serial Changes in Bone Scintigraphy and Plasma Phosphatases

Imaging group	*N.*	*Alkaline phosphatase groups*								*Acid phosphatase groups*							
		1	*2*	*3a*	*3b*	*4a*	*4b*	*5*	*6*	*1*	*2*	*3a*	*3b*	*4a*	*4b*	*5*	*6*
1	58	41	10		1		4	1	1	46	1		11				
2	13	3	4			2	3		1	10	2		1				
3*	18	3		3	5	5	1	1		4		2	8	1	3		
4	9		1			2	6			2	1			1	5		
5	15	2	2		3	7	1			6			4	1	2		2
6	14	1	1			9	3			3	4		1	1	5		
Total	127																

* Three patients in group 3 showed complete resolution of metastases on treatment.

treatment, reflecting response of advanced local and/or metastatic disease. In the remaining patients who developed a false positive plasma acid phosphatase, the single elevated level matched terminal clinical progression.

Group 2 Initially normal but subsequently positive imaging—"false positive" phosphatase levels

Six of the 13 patients had initially elevated alkaline phosphatase levels, perhaps giving an earlier indication of the presence of metastases than imaging. The mean duration of negative imaging was 18 months. In one patient abnormal isotope uptake was ascribed to Paget's disease. Definite metastases eventually became visible. Changes in plasma alkaline phosphatase reflected response to treatment and then relapse; this pre-dated the imaging.

Groups 2-6 Initial and/or subsequent positive bone imaging—"false negative" phosphatase levels

In 69 patients who exhibited positive bone images, only 3 showed complete regression of bone disease. Assuming the remainder had active metastases, 9 patients (13%) had false negative alkaline phosphatase levels. However, 6 of these clearly had very slowly progressive disease with long survival and in 3 patients alkaline phosphatase levels did fall in response to treatment but were within normal limits throughout. Many more patients with bone metastases at or subsequent to presentation had false negative acid phosphatase levels (36%).

Groups 3 and 4 Comparison between imaging and plasma alkaline phosphatase

From Table 2 it is apparent that in a high proportion of patients with metastases on treatment, plasma biochemical measurements could be classified in groups 3 and 4 (alkaline phosphatase 72%, acid phosphatase 50%) compared with the bone imaging (39%). Most of these patients showed a fall to within normal limits (3b, 4b), whereas complete resolution on the imaging was unusual. Seventeen patients with group 3 or 4 changes in alkaline phosphatase exhibited the "flare" phenomenon. This was not observed in the changes in acid phosphatase (Fig. 2).

Progressive sclerosis of osteolytic deposits Nine patients had a prominent osteolytic element in their bone metastases, shown on skeletal X-rays. On treatment the metastases often became easier to identify radiologically as their appearance altered to become more sclerotic. Conversely, lytic lesions could disappear as they became only sufficiently sclerotic to merge with their surroundings. In 5 patients the corresponding bone imaging showed diminished uptake of radiopharmaceutical, indicating healing, albeit temporarily. This interpretation was supported in all 5 patients by biochemical changes. In the remaining 4 patients with initially osteolytic metastases, a change to sclerosis was not registered on bone scintigraphy as a favourable response to treatment and the patients were classified as group 5 (2 patients) and group 6 (2 patients). However, a response was seen in the acid phosphatase levels of 3 patients and in the alkaline phosphatase in all 4 patients.

"Superscan" In 7 patients the uptake of radionuclide was so considerable that there was virtually total involvement of the parts of the skeleton examined (Perkins *et al.*, 1982). On the basis of the quantified data these patients were regarded as exhibiting favourable responses to treatment and were classified as group 3. In general this impression was supported by biochemical changes, but in 2 patients changes in plasma alkaline phosphatase could clearly be classified as group 4 (Fig. 3).

Hepatic component of plasma alkaline phosphatase Plasma gamma GT was sometimes elevated in patients with bone metastases, indicating hepatic dysfunction perhaps due to metastases. However, examination of isoenzymes invariably showed bone and liver components. When biochemical response to treatment was seen, gamma GT usually fell in parallel with the phosphatase levels.

Quantitative comparisons between imaging and plasma alkaline phosphatase In general the maximum plasma alkaline phosphatase level before or during treatment reflected the extent of bone metastases shown on the radionuclide images (Fig. 4).

Discussion

Radionuclide bone imaging remains the "gold standard" by which metastases are assessed in prostatic cancer. Biochemical evaluation by acid phosphatase determined enzymologically in plasma and/or bone marrow aspirate has proved relatively insensitive. The recently introduced radioimmunoassay techniques will almost certainly improve this but at the expense of low specificity, since advanced local disease in the absence of metastases will give positive results. Urine hydroxyproline may yet

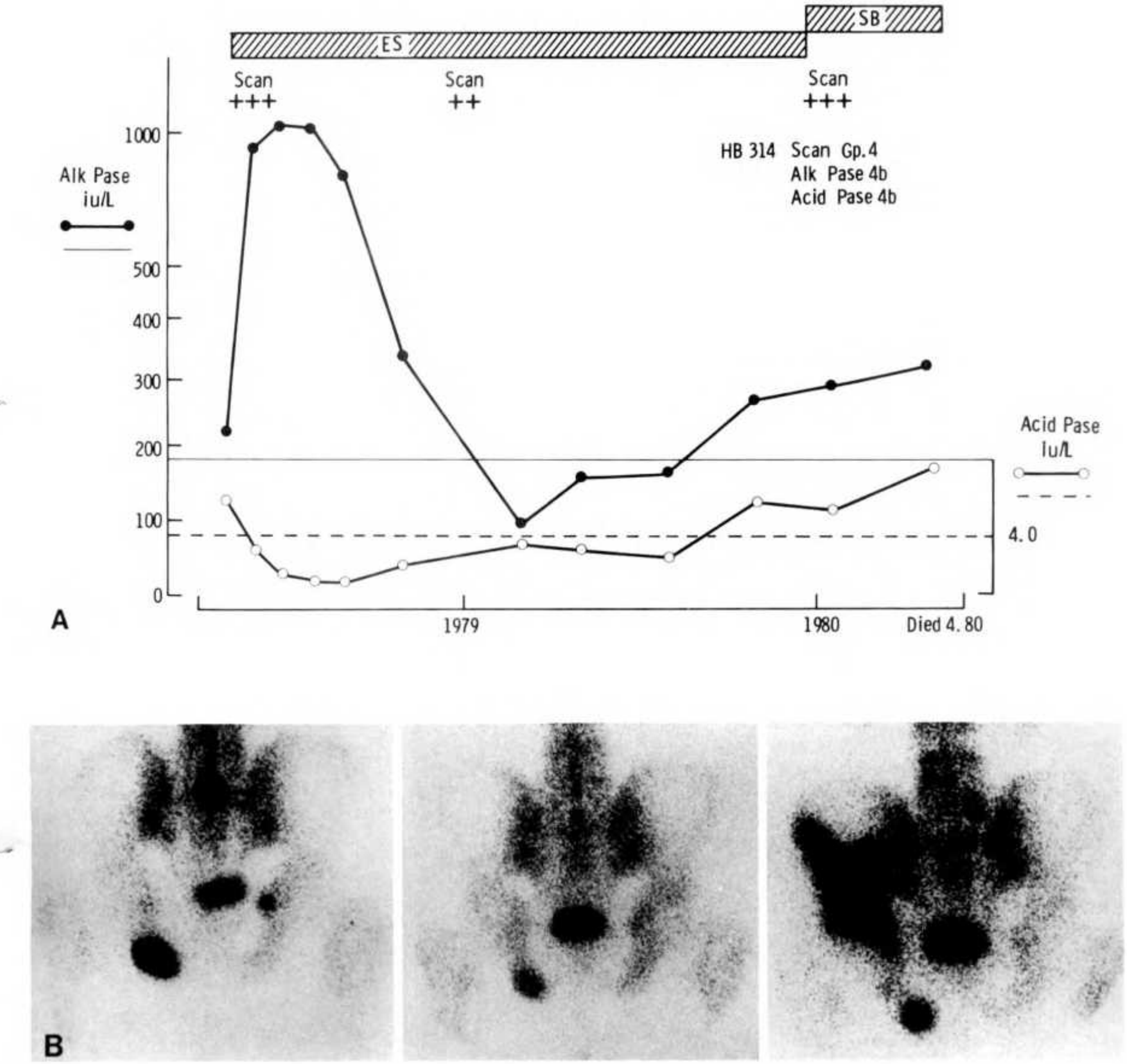

Fig. 2 Patient HB314 with extensive bone metastases treated initially with estramustine (ES) and then diethylstilboestrol (SB).
(A) Serial changes in plasma biochemistry (iu/l).
Alkaline phosphatase: Group 4b—with "flare".
Acid phosphatase: Group 4b.
(B) Serial bone imaging.
Metastases in pelvis initially improving, then deteriorating (Group 4).

prove a very satisfactory substitute for imaging, although the precautions during urine collection can introduce inconvenience and inaccuracies (Kontturi *et al.*, 1974; Mooppan *et al.*, 1983).

Surprisingly, plasma alkaline phosphatase has received little critical attention as a marker of bone metastases from carcinoma of the prostate. Jacobi and Hohenfellner (1982) and Murphy (1983) hardly referred to it and Fitzpatrick *et al.* (1978) dismissed it as a poor index of bone metastatic activity; yet data for comparison with radionuclide imaging were collated infrequently, so that important early changes outlined in the present study could have been missed. However, it is clear from the more detailed studies of Wajsman *et al.* (1978) and Killian *et al.* (1981) that the potential of

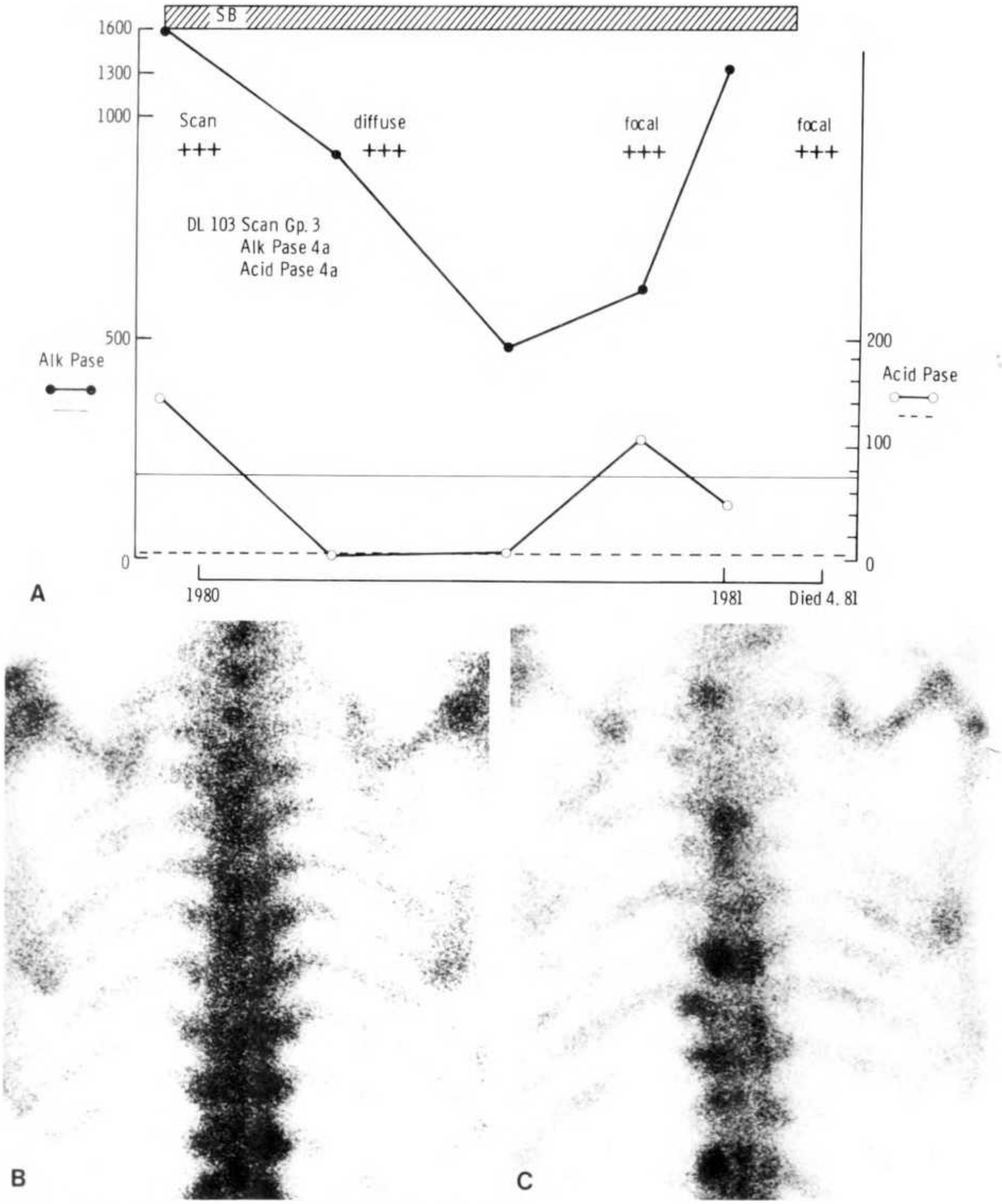

Fig. 3 "Superscan" patient DL103 treated with diethylstilboestrol.
(A) Serial changes in plasma biochemistry.
Alkaline phosphatase: Group 4a.
Acid phosphatase: Group 4b.
(B) Initial bone imaging showing diffuse changes in thoracic vertebrae.
(C) Image taken 10 months later showing focal uptake of tracer. Interpreted as improvement (Group 3).

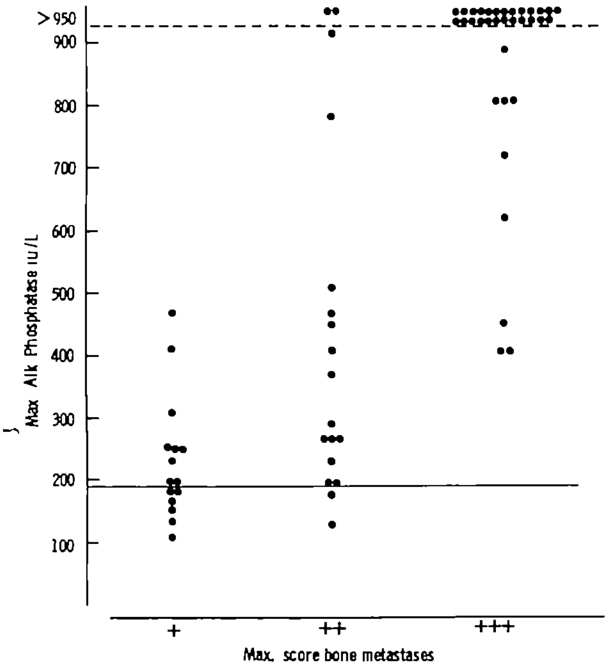

Fig. 4 Correlation between maximum plasma alkaline phosphatase and maximum score for bone metastases:
+ 1 metastatic focus
+ + 2 or 3 discrete foci
+ + + 4 or more discrete foci, or diffuse involvement.

alkaline phosphatase as a marker has been underestimated, and its sensitivity might be improved yet further by measuring its isoenzymes.

The division of bone imaging responses into six groups and the similar classification of phosphatase measurements provide an opportunity for close comparison between bone imaging and plasma biochemistry hitherto unexplored.

In the present study the patients were selected for evidence of advanced local disease (T3/4). It was therefore expected that a high proportion (44%) would have bone metastases at presentation or develop them in the course of treatment. However, the proportion was almost as great (43%) in a large series of patients with T1 to T4 disease reported in a VACURG study (Byar, 1977).

It is possible that the high rate of false positive phosphatase measurements (18%) in patients with negative bone images at presentation reflected an even higher rate of extra-osseous metastatic growth. Abnormal liver function tests provide some explanation for elevated alkaline phosphatase levels but certain factors such as bone pain did suggest that the raised levels indicated bone metastases in other patients. The impression that alkaline phosphatase may be more sensitive than bone imaging is supported by the high proportion of group 2 (imaging) patients who had elevated levels before the development of a positive image on treatment. On the other hand, the opposite view is suggested by 4 patients with bone metastases who presented with normal alkaline phosphatase levels which ultimately became elevated.

The false negative rate for alkaline phosphatase in patients with positive images was low and was mitigated further by the fact that metastatic disease was obviously relatively inactive in such patients. The much higher false negative rate for acid phosphatase is emphasised.

The fact that many more patients could be classified in groups 3 and particularly group 4 on a basis of phosphatase measurements rather than imaging suggests that a good response to therapy—albeit temporary—is more readily demonstrated biochemically and is more in line with the acknowledged sensitivity (approximately 80%) of prostatic cancer to hormone treatment (Resnick and Grayhack, 1975). Tha alkaline phosphatase "flare" is known to occur early as a marker of response to treatment in a variety of metabolic bone diseases. It has been reported in patients with prostatic malignancy (Huggins and Hodges, 1941; Killian *et al.*, 1981) but is usually overlooked as a valuable marker of treatment response. It was frequently seen in the present series of patients.

Classification of changes in the bone images can be confusing. One lesion can improve whilst fresh sites develop. The change from diffuse to focal uptake of radiopharmaceutical almost certainly indicates improvement but thereafter early recognition of deterioration can be difficult. Alkaline phosphatase has proved helpful in detemining the overall state of activity of bone metastases. Furthermore, it can reinforce conclusions drawn from skeletal images and X-rays on whether or not an area of sclerosis is a new lesion when osteolytic disease has predominated prior to treatment (Pollen and Shaler, 1979).

This study has demonstrated that plasma alkaline phosphatase is a much more reliable marker of bone metastases in prostatic cancer than acid phosphatase. An ideal protocol for studying such patients would include initial radionuclide bone imaging and X-rays of abnormal sites, followed by frequent estimations of plasma alkaline phosphatase during treatment. Complementary liver function tests and measurement of the contribution of bone and liver isoenzymes might be helpful, as it is possible that the absolute level of one or other can be elevated when total alkaline phosphatase concentration is normal (Wajsman *et al.*, 1978). This could account for some of the false negative values, particularly in patients with a low volume of relatively inactive metastases. It is probably less important to measure isoenzyme levels in patients with elevated total alkaline phosphatase and positive imaging since, biochemically, bone and liver components seem to respond similarly. The false positive elevation in a patient with negative bone imaging could be due to hepatic or intestinal disease and hence preponderance of the appropriate enzyme.

It could also be due to a benign form of bone disease or perhaps elevation of tumour derived placental (Regan) isoenzyme. This could be resolved by laborious analysis but in practice the result has little therapeutic consequence. Finally, false positive biochemistry may be due to false negative imaging. This is unlikely to be a major problem but it is certainly feasible since in the present study elevation of alkaline phosphatase sometimes preceded the change from negative to positive imaging in group 2 patients.

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The Authors

M. C. Bishop, MD, MRCP, FRCS, Consultant Urologist, Nottingham City Hospital.

J G Hardy, PhD, Senior Scientific Officer, Department of Medical Physics, Queens Medical Centre, Nottingham.

M. C. Taylor, FRCS, Consultant Urologist, Rotherham District Hospital

M. L Wastie, MRCP, FRCR, Consultant Radiologist, Queens Medical Centre, Nottingham.

R. J. Lemberger, FRCS, Senior Urological Registrar, Nottingham City Hospital

Requests for reprints to: M. C. Bishop, Department of Urology, City Hospital, Huckall Road, Nottingham NG5 1PB.

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Catheter-induced Urethritis: a Comparison Between Latex and Silicone Catheters in a Prospective Clinical Trial

J. N. NACEY, A. G. S. TULLOCH and A. F. FERGUSON

Department of Urology, Wellington Hospital, Wellington, New Zealand

Summary—A controlled randomised prospective study has been carried out on 100 male patients to compare the incidence of urethritis following catheterisation with either latex or silicone catheters. All patients underwent elective cardiac surgery and were catheterised for 48 h with antibiotic cover, and were followed up for 6 months post-operatively. Of those with latex catheters 22% developed urethritis, compared with 2% of those in the silicone catheter group. This difference is statistically significant ($P < 0.01$). Two of the former patients developed a decreased urinary flow and both had tight anterior urethral strictures.

Urethritis is a common sequel to urethral catheterisation, and in some cases this may progress to urethral stricture. Various factors have been thought to contribute towards the development of urethritis—such as the size and composition of the catheter, the type of lubricant used during insertion, and the duration of catheterisation (Edwards and Trott, 1973). In patients undergoing cardiopulmonary bypass surgery it has been suggested (Abdel-Hakim *et al.*, 1983) that hypothermia and reduced tissue perfusion of the urethra may be contributory factors.

In 1982, Ruutu and her co-workers reported an "epidemic" of urethral strictures in patients who had undergone open heart surgery. This observation was supported by similar reports from the United Kingdom, Ireland, Canada and Australasia (Smith and Neligan, 1982; Walsh, 1982; Wesley-James, 1982). These reports are retrospective and in some cases anecdotal. The authors, supported independently by Engel in 1983, believed that it would be useful to carry out randomised prospective studies in order to determine the factors responsible for urethritis and urethral stricture.

The aim of this study was to assess the effect of catheter composition on the incidence of urethritis and stricture. A brand of latex and a brand of silicone catheter were chosen for comparison.

Patients and Methods

All male patients over the age of 18 years undergoing elective cardiac surgery between 1 May and 30 November 1983 were considered for the trial. This minimum age was chosen to avoid the problem of the smaller calibre urethra in younger patients. Any patient who had had previous instrumentation or surgery to the lower urinary tract, or any history of urinary infection, was excluded. In the week before cardiac surgery the urinary flow rate was measured. At the time of surgery the patients were randomised into one of two groups. Using a table of random numbers each case was allocated a number in sequence—odd numbers to receive an 18F latex Foley catheter—even numbers an 18F silicone Foley catheter. The latex catheters were of the same brand from the same manufacturer. The silicone catheters were also identical, but were manufactured by a different company. Patients with a tight urethra were excluded from the trial. The catheters were inserted by medical staff using chlorhexidene antiseptic solution to clean the geni-

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talia, and 1% lignocaine lubricant jelly. Twenty ml of sterile water were placed in the balloon and the catheter connected to a closed drainage system. As part of the standard cardiac surgery protocol all patients received broad spectrum intravenous antibiotics during the 2-day period of catheterisation.

Follow-up consisted of close observation during the immediate post-operative period, with routine urine cultures, and swabs taken of any urethral discharge. The patients were reviewed 6 weeks post-operatively by the first author, the flow rate measured, and any lower urinary tract symptoms or signs recorded. The patients were also reviewed 6 months post-operatively and again any symptoms or signs recorded. All patients with urethritis has moderate penile discomfort and a purulent urethral discharge. The discharge was moderate in some but copious in others. The degree of early post-operative symptoms did not correlate with subsequent stricture formation. Patients with either urethritis or a reduction of urinary stream demonstrated by urinary flow rate, returned for ascending and voiding urethrography to assess progression to stricture formation.

One hundred and five patients were considered for inclusion in this study. Two died in the immediate post-operative period and one 8 weeks following surgery. Two developed acute urinary retention following post-operative catheter removal and required further catheter drainage. These five patients were excluded from the trial. This left 100 patients eligible for study, 50 in each group. All have been followed up for a minimum 6-month period.

Results

The two uncontrolled variables (patient age and type of procedure) which may influence the occurrence of urethritis were compared between the two groups and found to be not significantly different (Table).

The incidence of urethritis in the patients catheterised with latex catheters was 22% (11/50), compared with 2% (1/50) in the patients catheterised with silicone catheters. This difference in the incidence of urethritis is statistically significant ($P<0.01$, χ^2 with Yates correction).

In all cases the urethritis developed during the first 12 h of catheterisation and continued for 5 to 12 days. In all cases the CSU was sterile, with swabs of the urethral discharge showing the presence of pus cells with an insignificant growth of organisms. Only two of the 11 patients complained of decreased stream and they were the only two showing a reduction in urinary flow rate. Both patients had been troubled by urethritis following insertion of latex catheters. The flow rates performed 6 weeks post-operatively had reduced from 10 ml/s to 5 ml and from 21 ml to 7 ml, both showing an obstructed pattern. Both had tight anterior urethral strictures. Urethrography on all other patients who had been troubled by urethritis was normal. No further symptoms of urethritis or decreased urinary stream were encountered at the 6-month follow-up period.

Discussion

The urethral reaction to indwelling catheters has been the subject of extensive clinical interest. Early reports (Binder and Gonick, 1969) focused on encrustation and calcification of urethral catheters in patients maintained on long-term drainage. At that time a significant decrease in encrustation and calcification was seen in a group of patients with silicone compared with latex catheters. It was found that the use of silicone catheters decreased the interval between catheter changes, and it was proposed that trigonitis, meatitis and urethritis would be less likely to occur.

The anxiety that the composition of catheter material may be a cause of urethral inflammation has prompted considerable laboratory research.

Table Patient Variables

Catheter type	*Mean age*	*Age range*	*CAVG**	*Valve replacement*	*CAVG and valve replacement*	*Other*
Latex n = 50	52.9	20-71	43	6	1	0
Silicone n = 50	54.9	33-73	40	5	3	2

* Coronary artery vein graft.

The recent "epidemic" of strictures (Ruutu *et al.*, 1982; Syme, 1982; Walsh, 1982; Sutherland *et al.*, 1983) has reactivated the search for an effective *in vitro* or *in vivo* method to detect suspect catheter material. In a dog model, Engelbart *et al.* (1978) tested catheters of six different compositions, including silicone and latex. Their results showed no difference in the inflammatory response when catheters of different composition were tested. However, these catheters were in place for 6 weeks, and it is possible that by this time any inflammation caused by the release of substances from the catheter itself had disappeared, Graham *et al.* (1983) compared the toxicity of catheters in cell cultures with the rabbit muscle implant test, and a mouse systemic toxicity test. Their work suggested that some urinary catheters could release substances harmful to mammalian cells, and may contribute to the clinical reactions of urethritis and strictures. The results showed that the latex catheters they tested were more toxic than the non-latex ones. It is of interest that when they tested pure latex it was found to be non-toxic. Engel (1983) emphasised that cell culture toxicity tests are useful, but their relation to clinical safety has yet to be established. The final arbiter is the clinical result, and this emphasises the importance of studies in patients.

Keitzer *et al.* (1968) speculated that urethral strictures might be prevented with plastic catheters. They compared the post-operative urethral calibration of patients who had been catheterised with latex catheters and a new vinyl (korocath) catheter. They recorded urethral narrowing in 43% of the latex group compared with 10% of the plastic catheter group. This view was supported by Painter *et al.* (1971), who cystoscoped patients who had been catheterised with catheters of different composition. They recorded that the teflon and silastic catheters caused the least reaction and latex caused the most prominent reactions. They also made the interesting observation that the inflammatory response was decreased in patients whose catheter had been in place for longer than 6 weeks. Engel *et al.* (1972) performed a prospective randomised study comparing the use of latex and silastic catheters for intubation following Otis internal urethrotomy for stricture. Their results showed a lower incidence of urinary tract infection, urethritis and recurrent stricture with the use of silastic catheters. Although the period of intubation in this study was a minimum of 30 days, it was suggested that silastic catheters should be used for short-term catheterisation.

This experimental and clinical evidence supports the view that latex catheters may be more toxic than silicone ones. The results of our study have shown that urethritis following short-term catheterisation may be significantly reduced by the use of silicone catheters. Guess and Stetson (1968) have suggested that because of the variation in tissue response from one patient to another, it may not be possible to manufacture a catheter from a substance that will not cause any tissue reaction. However, the use of silicone catheters in this series has approached an acceptable minimal level of inflammation without stricture.

Cell culture toxicity testing has demonstrated a wide range of toxicity between catheters of different composition (Graham *et al.*, 1983). The latex catheter used in our study was tested by Graham and has a moderate to low toxicity in cell culture, which is consistent with the low incidence of stricture seen. The silicone catheter is non-toxic in cell culture, and again this is consistent with our clinical findings of a very low incidence of urethritis and no strictures.

The question of whether reduced tissue perfusion of the urethra during cardiopulmonary bypass may contribute to urethral damage remains unanswered. With silicone catheters any effect of low perfusion is not apparent. It is still possible, however, that low perfusion may exacerbate the effect of toxic constituents from the latex catheters on the urethral mucosa.

Until recently the greater cost and apparent minimal benefit of the silicone catheter has precluded its use for routine short-term catheterisation compared with the less expensive latex catheter. When one considers the problems of urethritis and stricture seen with latex catheters, the silicone catheters, despite their greater cost, should be considered cost effective and used for short-term catheterisation.

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The Authors

J. N. Nacey, MB, ChB, Senior Registrar in Urology.

A. G. S. Tulloch, FRCSE, FRACS, Consultant Urologist and Senior Lecturer in Surgery, Otago University.

A. F. Ferguson, FRCS, FRACS, Consultant Urologist.

Requests for reprints to: J N. Nacey, Department of Urology, Wellington Hospital, Wellington, New Zealand.

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Rat Peritoneal Implantation Test

A New Method for Tissue Toxicity Testing of Urinary Catheters

M. TALJA

Urological Unit, Second Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland

Summary—Severe urethral inflammatory reactions followed by strictures have been reported after short-term catheterisation with latex catheters since 1982. In this study a new method for assessing tissue toxicity is presented. It is based on the degree of inhibition of rat peritoneal foreign body reaction. Because the results are easier to interpret and more quantitative than those of the rabbit muscle implantation test, the rat peritoneal implantation test is recommended as a standard *in vivo* toxicity test.

Urinary catheters are generally considered safe non-toxic devices. However, in 1982 a number of severe urethral strictures after short-term catheterisation with latex catheters were reported (Frazer *et al.*, 1982; Ruutu *et al.*, 1982; Smith and Neligan, 1982; Syme, 1982; Wesley-James 1982; Sutherland *et al.*, 1983; Wilksch *et al.*, 1983). Evidence obtained from various cell culture toxicity tests of latex catheters suggested that such complications could have been caused by toxic substances in the catheters (Graham *et al.*, 1983; Ruutu *et al.*, 1985).

According to the British Standards (1979), urinary catheters are included in the same category for tissue toxicity as endotracheal tubes and intravenous cannulae. There is no international standard for urinary catheters.

The most commonly used method for biomedical testing of urinary catheters is the rabbit muscle implantation test according to the US Pharmacopeia XX. In the original model, four test and two control catheter strips are placed in the paravertebral muscles of a rabbit. Tissue reaction is examined macroscopically, and if necessary with a magnifying lens. Extension of the test includes histological evaluation (Wilsnack, 1976; Graham *et al.*, 1983). The test is negative if there is no more haemorrhage or reactive encapsulation around the test strips than around the controls. More recently, positive control strips have been recommended with this method (British Standards, 1979). The test has the limitation of being solely qualitative and the assessment of the results subjective.

Another common test method is the mouse systemic toxicity test (British Standards, 1979). In this method eluates from devices are injected intravenously and intraperitoneally to mice and any toxic effects observed. This test has also been criticised as insensitive and of little value in screening biomaterials in terms of safety (Graham *et al.*, 1983).

The granulation reaction of peritoneum to local irritants has been known since the early nineteenth century (Graser, 1895; Ladwig, 1928). It begins with fibrin accumulation within a few hours and is followed by leucocyte and fibroblast infiltration.

In this report a new method is presented where the foreign body reaction of rat peritoneum is used as a measure of the tissue toxicity of urinary catheters.

Materials and Methods

Healthy laboratory rats bred in a closed colony and weighing 200 to 300 g were selected as test animals. The animals were anaesthetised by intraperitoneal ketaminhydrochloride (40 mg/ml) in a

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100 mg/100 g body weight dose. The abdominal hair was shaved and the skin was treated with chlorhexidine-alcohol solution. Through a 1.5 cm midline laparotomy incision 3 cm long test and control catheter pieces were implanted in pairs into the paracolic space with a strictly aseptic technique. Silicone catheter pieces were used as control specimens because these were known to be non-toxic in cell culture (Graham *et al.*, 1983; Ruutu *et al.*, 1985) and in animal tests (Graham, 1983). The laparotomy incision was sutured in two layers with running sutures. The animals were sacrificed using ether and autopsied. Random intra-abdominal bacteriological cultures were taken. The growth of foreign body reaction in the lumen of the catheter pieces was washed out with 4% neutralised formaldehyde solution and fixed in transparent tubes. The reaction within the lumen of the catheter pieces was classified macroscopically and evaluated microscopically.

A preliminary investigation was carried out to determine the optimal duration of implantation. The animals were sacrificed between 1 and 9 days. A 4-day implantation period was selected for the definitive method because the extent of any reaction was most prominent then, allowing clear differentiation between catheters.

Because the catheters were of different sizes (12–20 F), the effect of this on the foreign body reaction had to be evaluated. Silicone tubes of various sizes (10-20 F) were implanted into the peritoneal cavity for a 4-day period and the reactions compared.

Various catheters were investigated by using six rats for one catheter batch. At the same time cell culture tests with human cell lines and rabbit muscle tests were carried out according to the US Pharmacopeia for these same batches.

Results

There was a great variation in the foreign body reaction caused by different catheters.

In the preliminary investigation the foreign body reaction at the end of Day 1 had invaded the lumen of control and well-tolerated catheters. The difference between well and poorly tolerated catheters was most marked on the fourth day. This implan-

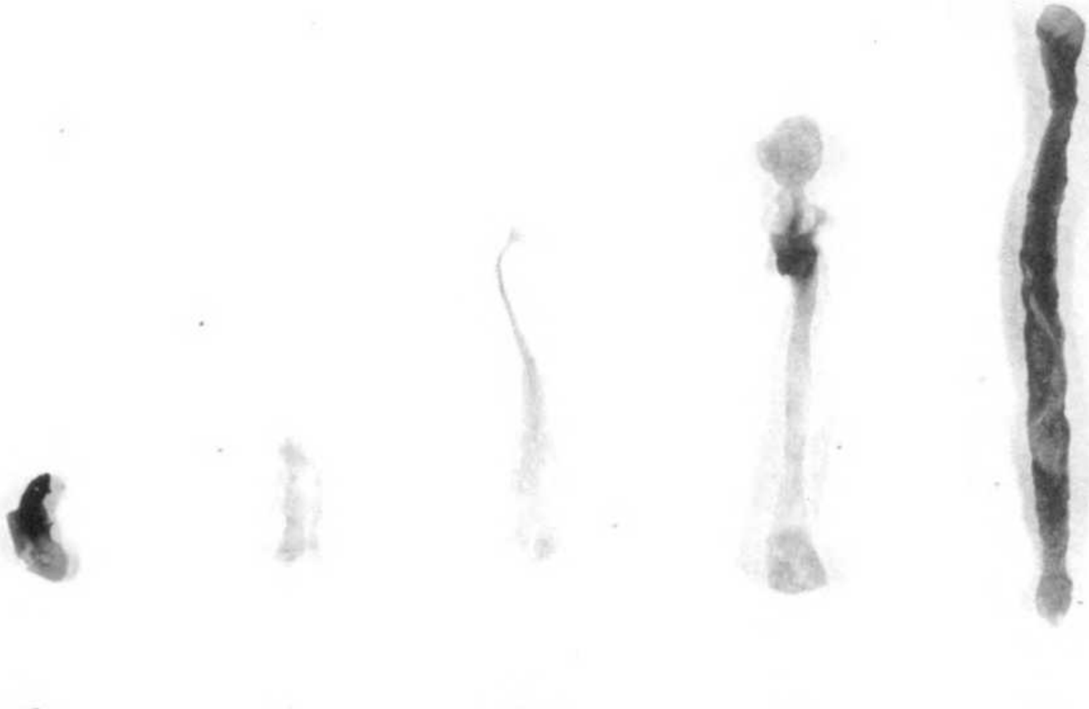

Fig. 1 Macroscopic findings of foreign body reaction. Formalin fixed specimens from various catheters representing growth grades 0 to 4.

tation period was therefore selected for the final test procedure.

The size of tube had no effect on the invasion of foreign body reaction into the lumen. There were some minor differences between different animals in individual reactions to the same catheter batches.

In the final test procedure, the macroscopic finding could be classified into five grades (Fig. 1):

Grade 0 No invasion of the foreign body reaction into the catheter lumen and/or necrotic omental adhesions to the cut ends of the catheter.
Grade 1 Slight grey growth (fibrin accumulation) with/without haemorrhage.
Grade 2 Less than half of the lumen filled with grey turbid growth.
Grade 3 The lumen filled from half to full length with turbid growth.
Grade 4 The lumen of implanted catheter pieces completely filled with turbid pink (vascularised) growth. (This foreign body reaction is undisturbed).

Microscopic findings

In the samples representing Grade 4 reaction the resorption of the fibrin network by polymorphonuclear leucocytes was advanced and already fibroblasts were seen. Lacunae for capillaries were forming (Fig. 2).

In samples representing Grades 0 and 1 reaction the extent of fibrin was slight and only a few leucocytes were invading it (Fig. 3). Between Grades 0 and 4 a sliding scale of foreign body reactions was seen and could be classified into three categories.

An adhesive reaction of omentum on to the outer surface of catheters was found in some samples. In the microscopic evaluation of these cases a leucocyte reaction with prominent granulocyte infiltration was seen at the sites of contact of omentum with the outer surface of catheters (Fig. 4). The bacteriological cultures were negative.

Discussion

When foreign material is introduced into the abdominal cavity it leads to the formation of adhesions. The fibrinogen in the exudate is activated to fibrin and this may occur within 3 h (Trompke and Siegner, 1956). Herzler (1915) reported that a fibrinous network began to develop in an injured area within 10 min of trauma and was fully developed after 2 h. The exudative phase is followed by organisation of the fibrinous material to fibrous adhesions by ingrowth of capillaries and fibroblasts (Graser, 1985; Ladwig, 1928; Myllärniemi, 1967). This fibrin dissolution begins by emigration of polymorphonuclear leucocytes almost immediately after injury (Riddle and Barnhart, 1954). Cameron *et al.* (1957) found that after 3 days the

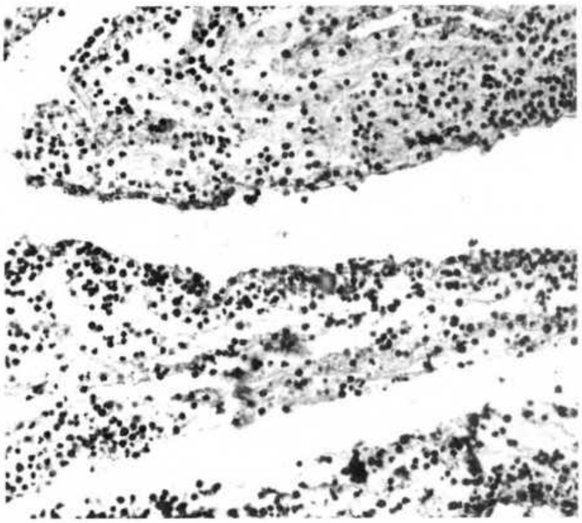

Fig. 2 Normal foreign body reaction inside a well-tolerated catheter. There is a fibrinous network on the base with a moderate polymorphonuclear leucocyte infiltration and a primitive capillary system (H and E × 210).

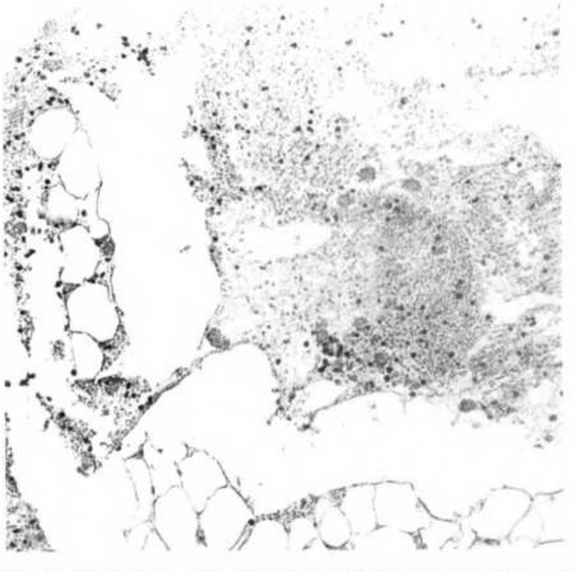

Fig. 3 Omentum at site of contact with the cut end of a poorly tolerated catheter showing fragmented fat cells, cell debris and a few inflammatory cells (H and E × 114).

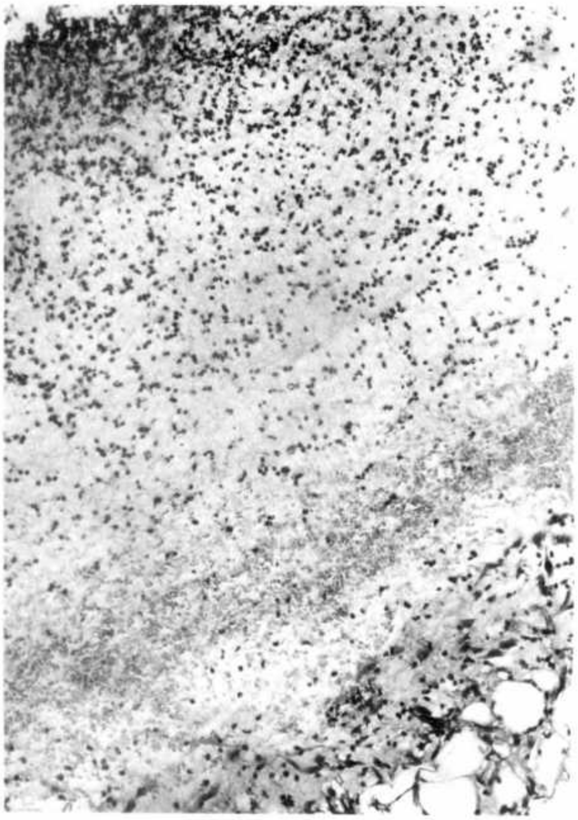

Fig. 4 Adhesive foreign body reaction. There is a purulent inflammation at the site of contact between omentum and the catheter with a fibrinous network and polymorphonuclear leucocyte accumulation. There is artificial haemorrhage in the deeper layers and fat vacuoles at bottom right (H and E × 120).

fibrinous tissue was replaced by fibrous tissue in intra-abdominal adhesions.

In the present work the foreign body reaction caused by intra-abdominally implanted lengths of urinary catheter was observed. Different reactions were found between various brands of catheter.

In the first part of the investigation, in which the implantation time varied, the lumen of control and well-tolerated catheter pieces was already filled with an accumulation of fibrin after 1 day's implantation, as in the normal uninhibited reaction process described above. The transparent fibrin became turbid with inflammatory cell infiltration and within a few days the lumen was filled with pink growth with fibroblast infiltration as described above. In contrast, in some other catheters there was little or no fibrin accumulation in the lumen after 9 days. A 4-day implantation period was selected for the definitive procedure because the difference between catheters was by then most marked in respect of the infiltration of reactive tissue into the lumen. In parallel with this, in the rabbit muscle test at least 72 h implantation is recommended (US Pharmacopeia XX).

The rat was selected for the test animal because the foreign body reaction of its peritoneum was most suitable for macroscopic evaluation compared with other laboratory animals. The rat is also easy to handle and expenses are low. A silicone catheter was chosen for the negative control specimen because there was no record of urethral sequelae with its use and it was found to be non-toxic in overlay cell culture and other animal tests (Graham *et al.*, 1983). Our group also found that it did not prevent cell multiplication in a modified cell culture test for tissue toxicity (Ruutu *et al.*, 1985).

We recommend that a control catheter be used in every animal to exclude the differences between individual animal reactions to foreign material. To eliminate possible statistical errors caused by incidental reactions, the number of test animals for one catheter sample was at least six rats. The reproducibility of the method was good, because the pooled variance was 0.78 when the whole scale of test analysis was from 0 to 5 with lowest mean 0.667 and highest mean 3.667. The foreign body reaction was not influenced by differences in the size of catheters (12-20 F). However, to eliminate possible errors due to variation in the total mass of the catheter it seems preferable to use catheters of the same calibre.

This study shows that some urinary catheters prevent the normal foreign body reaction in the peritoneal cavity of rats. The control catheters, known to be non-toxic, did not show this inhibitory effect. It may be that the substances dissolved from latex catheters are working as antithrombin agents. These findings are in agreement with cell culture tests (Ruutu *et al.*, 1985), where the inhibitory effect of some latex catheters on cell growth has been thought to be due to toxic substances (Graham *et al.*, 1983; Ruutu *et al.*, 1985).

An adhesive omental reaction interfered to some extent with the ingress of the foreign body reaction into the catheter lumen. In the most toxic catheters, according to the cell culture test, these adhesions were least and the invasion of foreign body reaction into the lumen was minimal or nil. This phenomenon may be due to properties of the catheter coating rather than a manifestation of toxicity.

The same catheter batches were tested additionally by the rabbit muscle implantation test according to US Pharmacopeia XX. The correlation between this test and the cell culture test done by our group was good.

It is concluded that the rat peritoneum implantation test is based on the degree of inhibition of peritoneal foreign body reaction. The results of the test are easy to evaluate macroscopically and they are semiquantitative. The reproducibility of the test is good, it is easy to perform and the costs are low.

Because the results are easier to interpret and more quantitative than those of the rabbit muscle implantation test, the rat peritoneal implantation test is recommended as a standard *in vivo* toxicity test method.

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The Author

M. Talja, MD, Registrar in Urology, Urological Unit, Second Department of Surgery, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki 29, Finland.

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Classification of Enlarged Prostatic Utricle in Patients with Hypospadias

F. IKOMA, H. SHIMA and H. YABUMOTO

Department of Urology, Hyogo College of Medicine, Hyogo, Japan

Summary—An enlarged prostatic utricle is often associated with hypospadias. To evaluate the relationship between the incidence of prostatic utricle and the degree of hypospadias, we performed retrograde urethrography and/or micturating cystourethrography on 280 patients with hypospadias. Prostatic utricles were demonstrated in 84 patients (27.5%) and the incidence increased according to the severity of hypospadias. The prostatic utricles were classified into four types from the standpoint of size and location of the opening of the utricle, and a direct relationship was demonstrated between the severity of hypospadias and increasing size of the prostatic utricle.

The prostatic utricle, a rudimentary structure present in the male prostatic urethra, is currently thought to be of mixed origin, with its cranial portion being derived from the müllerian duct and the caudal segment from wolffian and müllerian ducts and the urogenital sinus (Glenister, 1962). Enlargement of the prostatic utricle has been reported to be rare in the normal population (Moore, 1937) but it has often been demonstrated in patients with hypospadias and its incidence has increased according to the severity of the hypospadias (Howard, 1948; Shima *et al.*, 1979). Aetiological consideration of the prostatic utricle in relation to hypospadias suggests that an enlarged utricle *per se* reflects insufficient androgenic stimulation of the urogenital sinus and urethral groove (Devine *et al.*, 1980; Gonzalez-Serva *et al.*, 1981). The aim of this study was to present a new radiological classification of prostatic utricles according to their size and location of the opening as visualised on retrograde urethrocystography and/or micturating cystourethrography.

Patients and Methods

Three hundred and thirty-seven patients with hypospadias attended Hyogo College of Medicine between 1974 and 1983 and 280 of these underwent retrograde urethrocystography and/or micturating cystourethrography. Patients with chordee without hypospadias were excluded. Based on the urethrographic configuration, prostatic utricles were classified into four types (Fig.): Grade O: opening located on the posterior urethra but the utricle does not extend over the verumontanum; Grade I: larger than Grade O but it does not reach bladder neck; Grade II: more enlarged and its dome extends over the bladder neck. The prostatic utricle opens into the central area of the verumontanum in the prostatic urethra in Grades O, I and II. In rare cases the opening is situated in the bulbous urethra just distal to the external sphincter and this is classified as Grade III. In order to confirm the site of the utricular opening and the presence of the verumontanum in relation to the external sphincter, endoscopy was performed in selected cases. Further investigations included exploratory laparotomy, histological examination of relevant tissue and determination of chromosomal patterns, especially when intersex was suspected.

The term "vagina masculina" was used in this study only when a patient was found to have other unregressed paramesonephric duct structures (Devine *et al.*, 1980).

Results

The degree of hypospadias in 337 patients is shown

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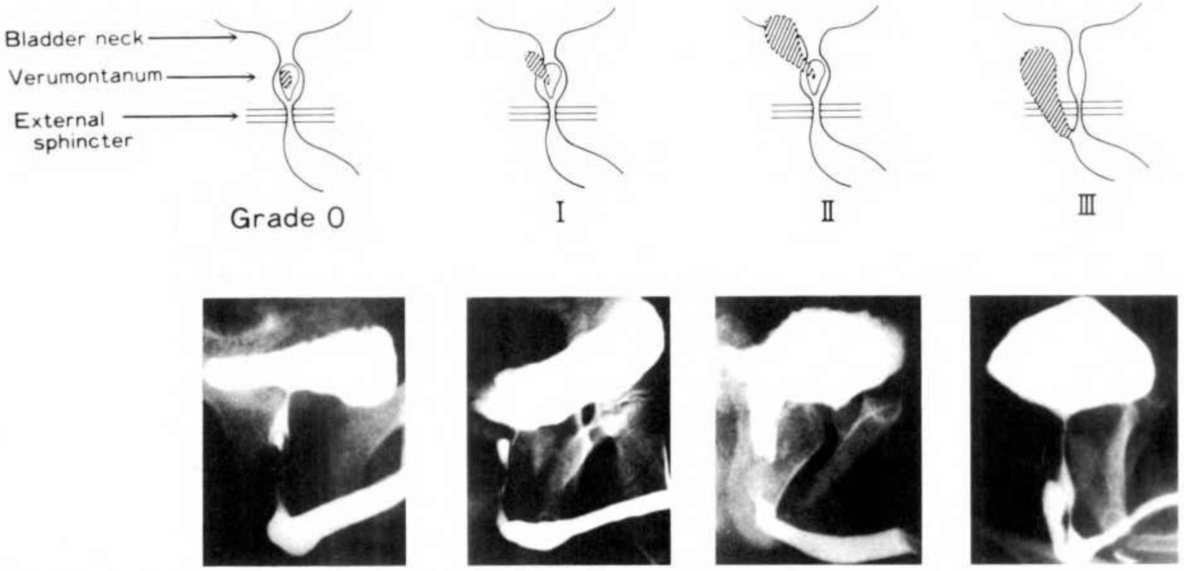

Fig. Classification of enlarged prostatic utricle by urethrography.

in Table 1. Seventy-seven (27.5%) of 280 patients with hypospadias who underwent urethrographic examination demonstrated prostatic utricles and the incidence increased in proportion to the severity of penile deformity (Table 2). Urethrographic grading according to the degree of hypospadias is shown in Table 3. The higher grades (II and III) were seen more often in patients with severe hypospadias. Grade II utricles occurred in 20% of 20 patients with penoscrotal hypospadias. Eight of 24 patients with scrotal hypospadias (33%) showed Grades II and III. Both patients with perineal hypospadias had Grade III utricles. Grade III utricles with unusual location of their openings were the same size as Grade II utricles and occurred only in patients with scrotal and perineal hypospadias.

Table 1 Degree of Hypospadias

Degree of hypospadias	*Number of patients*	(%)
Glandular	52	(15.4)
Penile	129	(38.2)
Penoscrotal	86	(25.5)
Scrotal	64	(20.0)
Perineal	6	(1.8)
Total	337	(100.0)

Table 2 Relationship Between Degree of Hypospadias and Incidence of Prostatic Utricle on Urethrography

Degree of hypospadias	*Number of patients*	*Prostatic utricle*	(%)
Glandular	41	7	(17.1)
Penile	108	24	(22.2)
Penoscrotal	69	20	(29.0)
Scrotal	57	24	(42.1)
Perineal	5	2	(40.0)
Total	280	77	(27.5)

Table 3 Urethrographic Grading of the Prostatic Utricle in Patients with Hypospadias

	Grade of utricle				
Degree of hypospadias	*O*	*I*	*II*	*III*	*Total*
Glandular	1	6	—	—	7
Penile	3	21	—	—	24
Penoscrotal	2	14	4	—	20
Scrotal	4	12	5	3	24
Perineal	—	—	1	1	2
Total	10	53	10	4	77

(Figures show the number of cases.)

There were eight cases of vagina masculina (Table 4) and they were categorised as intersex patients presenting with hypospadias. Four of these 8 patients were diagnosed as mixed gonadal dysgenesis with streak gonads on one side and persistent paramesonephric duct structures. One was a true hermaphrodite and 2 were male pseudohermaphrodites.

Table 4 Patients with Enlarged Prostatic Utricles and Paramesonephric Duct Structures (Vagina Masculina)

Patients	*Age at presentation*	*Condition*	*Chromosome*	*Location of urethral meatus*	*Grade of utricle*
S K	20 days	Mixed gonadal dysgenesis	46,XY	Scrotal	O*
K.S.	1 year 4 months	Mixed gonadal dysgenesis	46,XY	Scrotal	II
M.M	7 days	Mixed gonadal dysgenesis	46,XY	Scrotal	III
S M.	3 years 1 month	Male pseudohermaphroditism	46,XY	Scrotal	III
H.I.	12 years	Male pseudohermaphroditism	46 XY	Scrotal	II
H H	3 months	Male pseudohermaphroditism	46,XY	Scrotal	III
R K.	4 years 3 months	True hermaphroditism	46.XY	Scrotal	III
T F.	15 years	Mixed gonadal dysgenesis	45,X/46,XY	Scrotal	O*

* The opening of the vagina was situated on the prostatic urethra, but the entire structure was not filled sufficiently by contrast medium due to the narrow introitus The vagina and uterus of these patients showed hydrometrocolpos.

Discussion

The origin of a prostatic utricle is reported to be the paramesonephric duct for the cranial part, and the urogenital sinus, mesonephric and paramesonephric ducts for the caudal segment (Glenister, 1962). It has been postulated that enlargement might be caused by delayed regression of the paramesopheric duct and/or decreased androgenic stimulation of the urogenital sinus (Devine *et al.*, 1980). It is interesting that higher grade prostatic utricles (Grades II and III) were seen only in patients with severe hypospadias. This confirmed a direct relationship between the degree of hypospadias and the increasing size of the prostatic utricle observed by Howard (1948) and Devine *et al.* (1980).

The degree of enlargement of the prostatic utricle in patients with hypospadias may be considerably affected by the level of androgen at the critical time of organogenesis in the male mammalian embryo, for one cause of hypospadias is insufficient androgenic action during the period of androgen-dependent differentiation of the genitalia (Aarskog, 1970; Jones and Scott, 1971; Imperato-McGinley and Peterson, 1976). In fact, prepubertal boys with more severe degrees of hypospadias had poor interstitial cell testicular function compared with normal control boys on a human chorionic gonadotrophin load test (Shima *et al.*, 1981).

Incomplete regression of the paramesonephric duct for the cranial part of the prostatic utricle is caused by insufficient action of a different fetal regressor, the "müllerian inhibiting substance" (Jost, 1946a and b, 1947). In such cases müllerian duct structures such as the fallopian tubes, uretus and upper third of the vagina are basically recognised.

Howard (1948) and Devine *et al.* (1980) considered a prostatic utricle to be enlarged when a cystoscope could be introduced into the lumen of the utricle for at least 2 cm. Although endoscopy is required in selected cases to determine whether a cervix uteri coexists or not, a urethrogram is more effective at visualising the size and location of the utricular opening except in the rare cases with a very narrow opening (Table 4). However, there were no convenient radiological standards by which to classify prostatic utricles according to size and location of the opening into the urethra. The present urethrographic grading system is useful in assessing utricular configuration.

The spectrum of radiological variation of prostatic utricles is not yet known and it is difficult to decide whether Grade O utricles should be included or whether they are a normal variation. Very few normal males revealed an enlarged prostatic utricle on urethrography (Moore, 1937; Edling, 1949). In our experience, 2 of 96 patients with cryptorchidism had Grade O prostatic utricles on urethrography.

Prostatic utricles with their opening located distal to the external sphincter (Grade III) were seen only in patients with scrotal or perineal hypospadias, which suggests a feminising tendency in these cases probably due to insufficient androgenic action during organogenesis in the embryo.

This new radiological grading system has proved useful in assessing the degree of utricular configuration associated with hypospadias and a direct relationship has been noted between the severity of hypospadias and the increasing size of the prostatic utricles.

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The Authors

F. Ikoma, MD, Director and Professor of Urology
H. Shima, MD, Instructor in Urology.
H. Yabumoto, MD, Urologist

Requests for reprints to: F. Ikoma, Department of Urology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663, Japan.

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Intravenous Urography as a Routine Investigation in Epididymitis

M. S. MURSHIDI

Department of Special Surgery, Urology Section, University of Jordan, Amman, Jordan

Summary—One hundred and forty-two patients were admitted to the Jordan University Hospital with acute epididymitis between 1973 and 1983. Sixty-five had intravenous urograms which revealed renal tuberculosis in 1 patient, renal or ureteric stones in 10, bladder neck obstruction in 3, unrelated congenital anomalies in 10 and no abnormalities in 41.

Twelve patients developed epididymal abscesses.

Compared with the other male organs of reproduction, it is probably true to say that the epididymis has been neglected by research workers and clinicians (Glover, 1982). As indicated in the *British Medical Journal* (1981), acute epididymitis may result from the extension of infection in the urinary tract, although haematogenous spread may be the mechanism in viral infections or tuberculosis. The latter condition should always be considered in the differential diagnosis of scrotal swellings even in the absence of previous tuberculosis (Ferrie and Rundle, 1983). Acute inflammation of the epididymis may be complicated by abscess formation (Mittemeyer *et al.*, 1966).

The purpose of this work is to emphasise that not all cases of acute epididymitis resolve and that some of them progress to abscess formation. It also underlines the difficulty in obtaining bacterial information about epididymal abscesses and discusses the value of routine intravenous urography in patients with epididymitis.

Patients and Methods

One hundred and forty-two patients who were diagnosed clinically as suffering from acute epididymitis were admitted to the Jordan University Hospital between 1973 and 1983. Their ages ranged from 17 to 55 years and two-thirds were less than 40 years old. Sixty-five patients had intravenous urograms and 12 developed an epididymal abscess as a complication of acute epididymitis.

Mid-stream specimens of urine and pus from the abscess were cultured for aerobic bacteria by standard methods in all 12 patients; staining and culture for tuberculosis and gonorrhoea were also carried out. The time at which the abscesses developed varied from 6 to 60 days from the time the clinical diagnosis of epididymitis was made (Table 1).

Treatment was by bed rest, scrotal support and antibiotics in all patients. It was started immediately after the diagnosis was made but some of the antibiotics were changed if the culture was positive and the sensitivity of the bacteria had changed. Ampicillin plus cloxacillin, ampicillin and cephradine were the main antibiotics given to these patients; there were no differences in the antibiotics

Table 1 Duration in Days between Clinical Diagnosis of Acute Epididymitis and Abscess Formation in 12 Patients with Epididymal Abscess

Duration in days	*Number of patients*
0–9	2
10–19	2
20–29	2
30–39	3
40–49	1
50–59	1
60–69	1

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given to those with abscesses compared with those who did not develop abscesses. The abscesses were drained surgically in nine patients and ruptured spontaneously in three.

Results

Abscess formation complicating acute epididymitis occurred in 12 of 142 patients (8.5%). Routine aerobic culture of the urine was negative in 9 of the 12 patients (75%) (Table 2). Culture of pus from the abscesses was negative in six patients (50%) (Table 3). The staining and culture of the urine and pus for tuberculosis and gonorrhoea gave negative results in all 12 patients.

Sixty-five patients had intravenous urography (Table 4) which revealed renal tuberculosis in 1, renal or ureteric calculi in 10, bladder neck obstruction in 3 and unrelated congenital abnormalities in 10. Forty-one patients had no abnormality.

Table 2 Results of Routine Aerobic Bacteriological Culture of Mid-stream Urine in 12 Patients with Epididymal Abscess

Bacteria	*Number of patients*
Negative	9
Escherichia coli	2
Proteus	1

Table 3 Results of Routine Aerboic Bacteriological Culture of Pus in 12 Patients with Epididymal Abscess

Bacteria	*Number of patients*
Negative	6
Escherichia coli	4
Proteus	1
Pseudomonas	1

Table 4 Urinary Tract Abnormalities in 65 Intravenous Urograms Performed on Patients with Epididymitis

Abnormality	*Number*
Renal tuberculosis	1
Renal or ureteric calculus	10
Duplex renal system	4
Signs of bladder neck obstruction	3
Bladder diverticulum	2
Horseshoe kidney	2
Ectopic kidney	1
Congenital pelviureteric obstruction	1
Total	24

Discussion

The incidence of abscess complicating acute epididymitis is higher in this series (8.5%) than the 3% reported by Mittemeyer *et al.* (1966) and the 1% by Gartman (1961). Delayed and inappropriate therapy are important factors in abscess formation (Gartman, 1961). Microabscesses and acute tubular destruction of the epididymis were reported in young men with acute "idiopathic" epididymitis (Wolin, 1971). Acute epididymitis may result from prostatic and urogenital infections (Handley, 1946). *Chlamydia trachomatis* is a frequent cause of non-gonococcal and post-gonococcal urethritis in males (Holmes *et al.*, 1975). Berger *et al.* (1978) reported a high prevalence of non-gonococcal urethritis in men with acute epididymitis and *Chlamydia trachomatis* was isolated from the urethra and epididymal aspirates in many of their patients. Berger *et al.* (1979) found an association with *Chlamydia trachomatis* infection in two-thirds of men aged under 35 years who were suffering from "idiopathic" epididymitis. The infection was often accompanied by azoospermia or oligozoospermia.

Because of the high incidence of negative findings on routine bacteriological studies in this series, most of our patients were in the "idiopathic" group of patients with acute epididymitis complicated by abscess formation.

Kalovidouris *et al.* (1982) advocated intravenous urography in patients with acute epididymitis if there was evidence of past or present tuberculosis. Genito-urinary tuberculosis extends from one part of the genito-urinary system to the other (Medlar *et al.*, 1949) and tuberculous infection may spread to the epididymis through the vas deferens or via the bloodstream or lymphatics (Winblad, 1975). However, Mittemeyer *et al.* (1966) reviewed 610 cases of epididymitis and found only 5 cases of tuberculosis.

Our findings on intravenous urography are similar to those of Kalovidouris *et al.* (1982) if tuberculosis is suspected, but we found many renal or ureteric stones and they did not. The finding of 10 patients with stones in our study reflects the increasing prevalence of renal stones in many parts of the world (Blacklock, 1982).

It is concluded that not all cases of acute epididymitis settle, and a proportion of them proceed to abscess formation. Intravenous urography is necessary only if there is a history of tuberculosis or evidence of stones or calcification within the urinary tract.

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The Author

M S. Murshidi, FRCS, Assistant Professor of Urology, Jordan University Hospital, Amman, Jordan.

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Bladder Electromyograms and Function in Monkeys after Atropine

M. D. CRAGGS and J. D. STEPHENSON

MRC Neurological Prosthesis Unit and Department of Pharmacology, Institute of Psychiatry, London

Summary—Voiding induced in conscious monkeys by infusion of sterile saline into the bladder via a chronically implanted bladder catheter was stable over many months. Artefact-free recordings of electrical activity were obtained from the bladder neck and dome of these animals during bladder filling and voiding. Characteristic voiding electromyograms were recorded from both sites but were seen first in the record from the neck. Small doses of methyl-atropine abolished both voiding and the electromyograms; evoked responses to sacral ventral root stimulation were similarly prevented. Therefore the bladders of both man and monkey are very sensitive to atropine, unlike the bladders of most other animals.

The observation of Cullumbine *et al.* (1955), that soldiers given atropine were unable to void, contrasts with the commonly reported results obtained in experimental animals that urinary bladders are relatively insensitive to cholinoceptor blockade (Langley and Anderson, 1895; Taira, 1972; Craggs and Stephenson, 1982). However, Brindley and Craggs (1975) showed that in the monkey bladder, contractions evoked by sacral ventral root stimulation were sensitive to atropine, suggesting a significant difference between bladders from primates and from other eutherian mammals.

The present study compares the effect of atropine on voiding in the conscious monkey with its effect on rises in bladder pressure evoked by electrical stimulation of sacral ventral roots. The electromyographic activity of the bladder neck and dome was also recorded in an attempt to differentiate functionally the two regions; it is known that the parasympathetic influences on the bladder neck of monkeys are insensitive to atropine (Brindley and Craggs, unpublished results).

Methods

Conscious voiding preparations. Experiments were performed on two rhesus monkeys (wt 6 kg), one of each sex. The monkeys were anaesthetised with sodium pentobarbitone (36 mg/kg im) and prepared for aseptic surgery.

A silicone rubber catheter (2.5 mm od, 1.5 mm id) was implanted chronically into the bladder. The distal end was led subcutaneously to emerge at the skull where it was secured for external connection as previously described for cats (Shaffer *et al.*, 1979). Pairs of insulated platinum electrodes (0.07 mm diameter) were inserted into the detrusor and bladder neck to record electromyograms (Craggs and Stephenson, 1976). The animals were allowed to recover for at least 1 week before experiments and the bladder catheter was flushed daily with sterile saline.

During experiments the monkeys sat in a primate chair and sterile saline was infused into the bladder (5 ml/min) via the catheter. The volume and interval between each voiding were recorded. Typical control voidings were in the range 20 to 30 ml, which is usual for unrestrained rhesus monkeys (Feldmahn *et al.*, 1960). EMG activity was recorded via a low noise cable and standard physiological amplifiers (Craggs and Stephenson, 1982).

Anaesthetised preparations. The monkeys (baboons and rhesus monkeys) were part of a series of studies and had chronically implanted sacral

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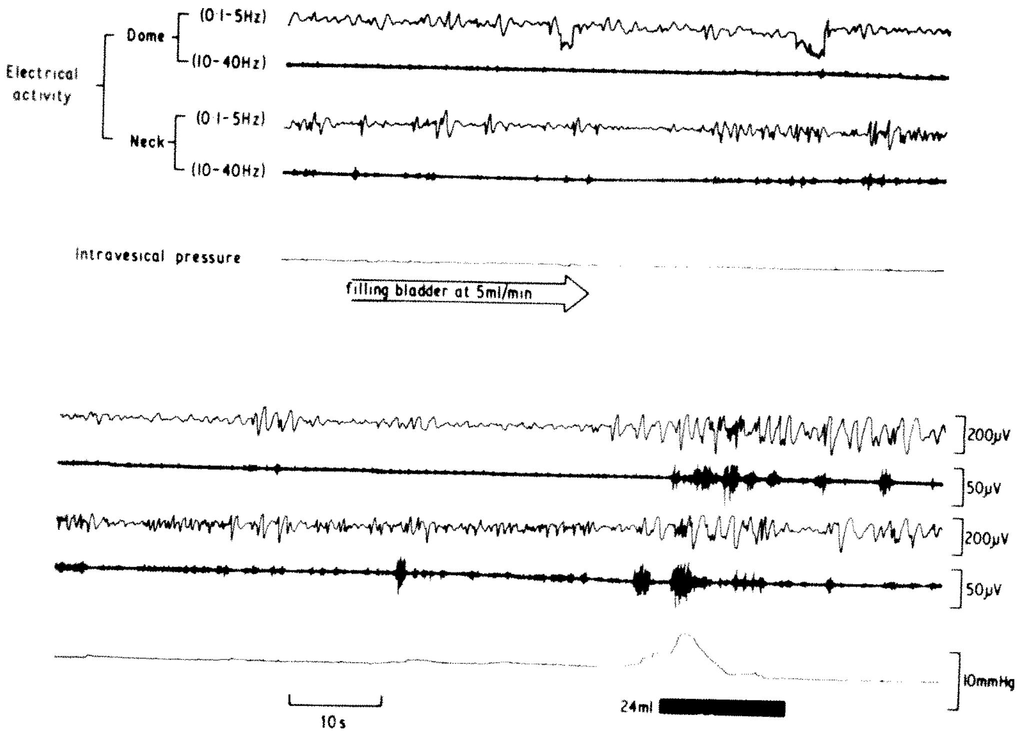

Fig. 1 Continuous recording of electrical activity from the bladder neck and dome to show micturition, indicated by black bar, induced by infusing saline into the bladder. Voiding lasted approximately 20 s and was accompanied by a rise in intravesical pressure. The higher frequency band (10-40 Hz) represented the electromyograms and reliably indicated bladder pressure rises and voiding.

root electrodes (Brindley and Craggs, 1975). For these experiments, the monkeys were anaesthetised with sodium pentobarbitone (36 mg/kg im). A sterilised catheter was introduced into the bladder via the urethra for infusion of saline and recording of intravesical pressure. At the end of each experiment the catheter was withdrawn and the monkeys were allowed to recover. Electromyographic activity was recorded through the implanted bladder electrodes.

Drugs used. These were atropine sulphate and atropine methylnitrate. Atropine methylnitrate was used for the experiments in conscious animals because it penetrates the blood brain barrier less readily and therefore minimises the adverse central effects of cholinergic blockade.

Results

Experiments on conscious monkeys

Sterile saline infused into the bladder of conscious monkeys for periods of up to 3 h via chronically implanted bladder catheters induced regular voiding. The volume of a single voiding ranged between 20 and 30 ml. From knowledge of the infusion rate and average urine production, residual volumes were determined and found to be negligible.

Figure 1 is a record of electrical activity recorded from the bladder neck and dome during a cycle of micturition. Electromyograms (10–40 Hz) were almost entirely absent during the filling phase but voiding was anticipated by activity in the neck followed by simultaneous electromyograms at both sites throughout voiding. Low frequency activity (0.1-5 Hz) previously reported as being contaminated by artefact (Craggs and Stephenson, 1976) was far less discriminatory for events at the time of micturition and did not clearly reveal any further difference between neck and dome. Five consecutive voidings from the same animal are shown in Figure 2.

Effects of methyl atropine. Methylatropine (0.1 mg/kg) reduced the volume of each voiding from 20 to 25 ml to less than 10 ml with increasing residual volumes (estimated as described above). During this period of retention the animal attempted to void more frequently. After a few

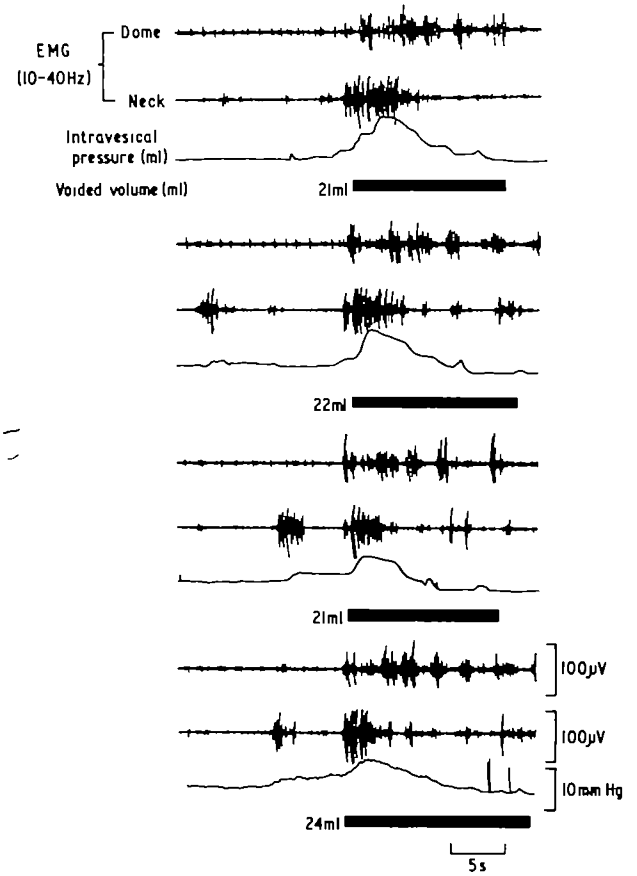

Fig. 2 Electromyograms and associated intravesical pressure rises during five consecutive voidings Electrical activity recorded from the neck usually preceded that from the dome by a few seconds.

such attempts the saline infusion was stopped and the bladder emptied via the catheter. The effect of methylatropine on the pattern of voiding was associated with much reduced rises in intravesical pressure and loss of electromyographic activity in both the neck and dome (Fig. 3).

Experiments on anaesthetised monkeys

Supramaximal electrical stimulation of the sacral ventral roots for 15 s produced a rise in intravesical pressure which reached a peak towards the end of the stimulation period. The maximal rise could be maintained with minimal fatigue during prolonged stimulation. Atropine (0.006 mg/kg iv and 0.034 mg/kg iv) produced a dose-dependent reduction in the pressure rise evoked by sacral ventral root stimulation (Fig. 4). The results from 8 monkeys are shown in Figure 4b. The evoked bladder electromyogram (Craggs and Stephenson, 1976) and the associated rise in bladder pressure was also completely abolished by atropine 0.05 mg/kg iv (Fig. 5).

Discussion

The results obtained in monkeys confirm the observation made in man (Cullumbine *et al.*, 1955) that muscarinic receptor blockade abolishes the ability of some primates to void. After methylatropine and atropine the monkeys made frequent attempts to void, suggesting that the drugs did not affect central awareness of the need to void. The primate bladder therefore exhibits a much greater sensitivity to cholinoceptor blockade, previously shown in anaesthetised monkeys (Brindley and Craggs, 1975), than has been observed in other laboratory animals (cat, dog, guinea-pig, *etc.*). In dogs and cats the partial antagonism by atropine and hyoscine of rises in intravesical pressure, evoked by electrical stimulation of sacral parasympathetic nerves, was more pronounced at the end of the period of stimulation than at the beginning (Henderson and Roepke, 1934; Craggs and Stephenson, 1982). To explain this difference Henderson and Roepke (1934) proposed that the response comprised an initial and a late component, only the second being cholinergic. Possible candidates for the non-cholinergic non-adrenergic transmitter responsible for the initial phase of the response have been discussed by Ambache and Zar (1970) and by Burnstock *et al.* (1972). No evidence was obtained for a similar distinction to be made in primates because atropine abolished the whole response and with it the need to postulate involvement of other transmitters. Moreover, the evoked electromyogram, in which an initial component is likely to be especially prominent, was very sensitive to cholinoceptor blockade in monkeys; this component is resistant to atropine in cats (Craggs and Stephenson, 1976). Nevertheless, it is possible that under certain pathological conditions other substances known to be present in the human bladder, *e.g.* various peptides, prostaglandins, *etc.*, may contribute to the bladder activity. However, in paraplegic man, for example, the results of stimulating the sacral ventral roots (Rushton, personal communication) also demonstrate that the bladder is very sensitive to atropine.

In contrast to its effects on the detrusor, atropine does not interfere with urethral relaxation evoked by sacral ventral root stimulation in primates (Brindley and Craggs, unpublished results); in cats, urethral relaxation is sensitive to the β-adrenoceptor antagonist propranolol, suggesting mediation

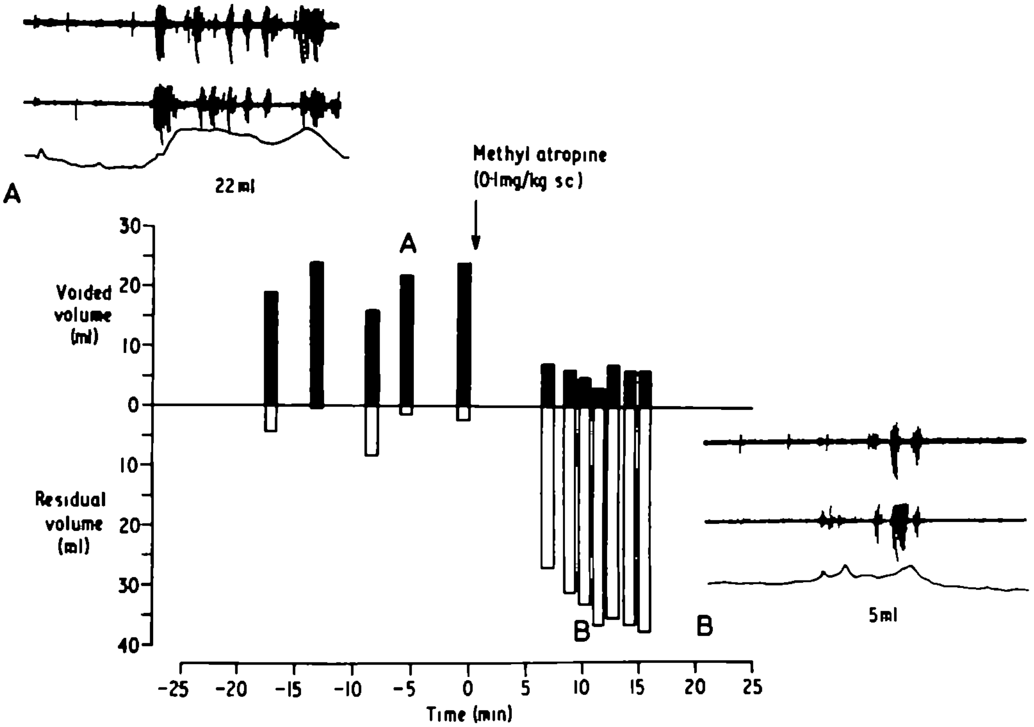

Fig. 3 Effects of peripheral cholinoceptor blockade with methylatropine (0.1 mg/kg sc) on voided and residual volumes. Methylatropine impaired the monkey's ability to empty its bladder completely, leading to a gradual increase in residual volume. Electromyograms from the dome (upper record) and neck (middle record) and bladder pressure traces are shown for two representative voidings: (A) before and (B) after methylatropine.

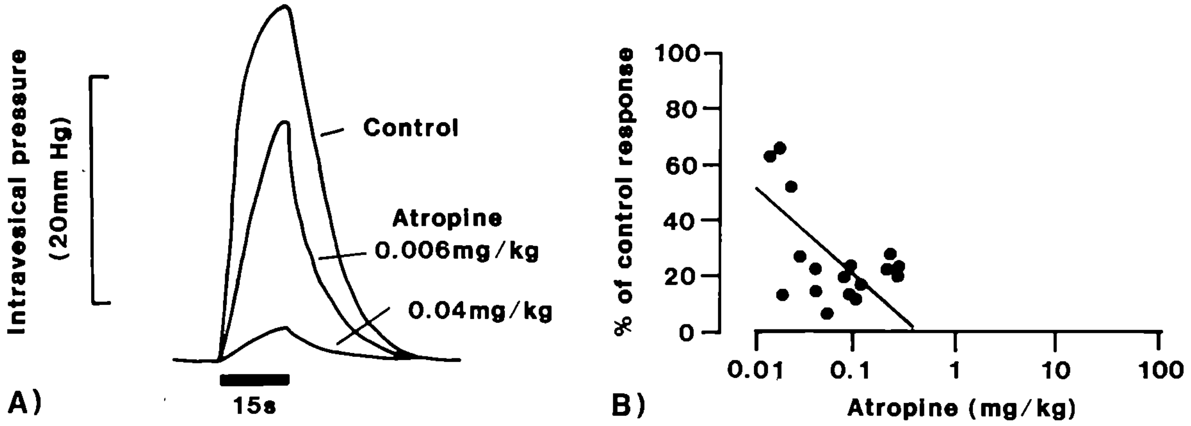

Fig. 4 Dose-dependent reduction in the intravesical pressure rise evoked by sacral ventral root stimulation of anaesthetised monkeys after atropine. The present records (A) were obtained from a single animal and the graph (B) shows results from 8 animals.

by intramural adrenergic nerve fibres (McGuire, 1977). This innervation is quite separate from the classical sympathetic innervation arising in the thoraco-lumbar spinal cord and which is responsible for the α-adrenoceptor mediated contraction of the bladder neck. However, if such a contraction of the bladder neck did occur between voidings, then this was not evident from the electromyographic record. This confirms the finding in cats (Craggs and Stephenson, 1982). In an attempt to differentiate muscle activity in the bladder dome from that in the neck, electromyograms were

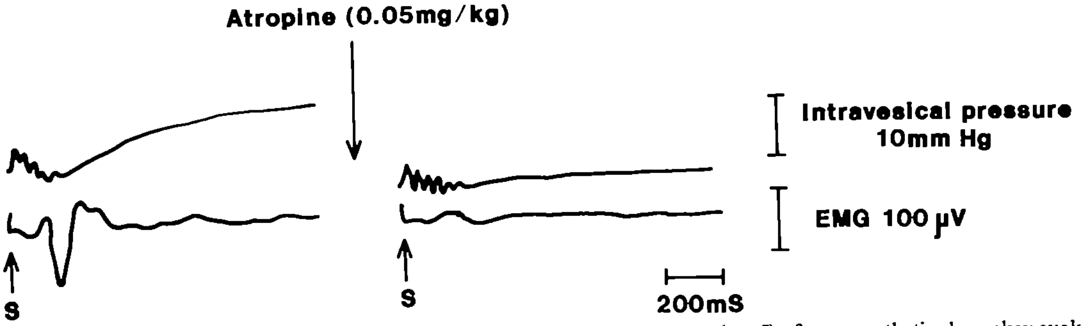

Fig. 5 The effect of atropine (0.05 mg/kg) on the averaged bladder electromyogram (n = 5) of an anaesthetised monkey evoked by sacral ventral root stimulation. The urethral movements reflected in the intravesical pressure trace were not affected by atropine.

obtained from these two regions of the bladder; movement artefacts, to which electrical recordings in this region are particularly prone, were removed by filtering out frequencies below 10 Hz (Craggs and Stephenson, 1976). While voiding was anticipated by activity in the neck region followed by activity in the dome, there was no evidence for a selective action of atropine on recordings obtained from the detrusor. If the electromyogram in the neck was generated in longitudinally oriented muscle then its early contraction would cause bladder neck opening in advance of a contraction of the main body of the bladder. Unfortunately we were not successful in placing recording electrodes more distally into the proximal urethra, where such an effect was likely to be more pronounced.

Electromyograms similar to those described have been obtained in patients suffering spinal injury (Nanninga and Kaplan, 1978). However, because the electromyogram and associated muscle contraction are so intimately linked, the main diagnostic use of the electromyogram will probably be in identifying regions of the bladder which may be either denervated or decentralised.

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The Authors

M D. Craggs, PhD, Scientific Staff, MRC Neurological Prosthesis Unit and Senior Lecturer, Department of Physiology.

J. D. Stephenson, PhD, Senior Lecturer, Department of Pharmacology.

Requests for reprints to· M. D. Craggs, MRC Neurological Prosthesis Unit, Institute of Psychiatry, De Crespigny Park, London SE5 8AF.

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Ultrasound Examination of the Scrotum

M. J. MICHELL, P. M. THOMPSON, A. J. YATES BELL, J. P. PRYOR and D. A. PACKHAM

Departments of Radiology and Urology, King's College Hospital, London

Summary—The technique of real time ultrasound examination of the scrotum is described. The examination was performed on 120 patients and was found to be a helpful diagnostic aid in scrotal swelling and in the acute painful scrotum. It is recommended as a useful investigation for scrotal abnormalities.

Most hospitals have ultrasound facilities but ultrasound examination of the scrotum has only recently become a routine investigation. The experience of ultrasound in the investigation of scrotal pathology has recently been described by several authors (Leopold *et al.*, 1979; Orr and Skolnick, 1980; Carroll and Gross, 1983). We report our experience based on 120 examinations carried out over the last 18 months.

Method

The examinations were performed by a radiologist using general purpose real time sector scanners, Diasonics RA-1 and DRF-1 with 3.5 MHz or 5 MHz probes.

The patient was examined in the supine position with adhesive strapping over the thighs to support the scrotum. Scanning was carried out through a water bath consisting of a 500-ml saline bag placed between the ultrasound probe and the scrotal skin, to ensure that the region of interest lay within the focused part of the ultrasound beam. The time gain compensation curve was set low to adjust for the low sound attenuation of testicular tissue. A series of longitudinal, transverse and oblique scans was obtained.

Results

The ultrasound findings and final clinical diagnosis are summarised in the Table.

The normal testis has a smooth, oval outline and homogeneous echo pattern (Fig. 1). A small amount of fluid can often be seen adjacent to the upper pole of the testis. The head of the epididymis is seen as an area of relatively bright echoes above the upper pole of the testis. The body and tail of the

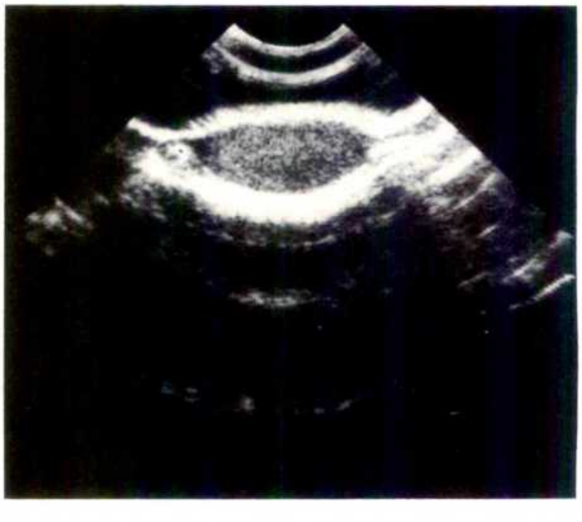
Fig. 1 Normal testis with head of epididymis above the upper pole. Longitudinal scan.

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984

Table Scrotal Ultrasound Results in 120 Patients

Ultrasound Findings		Final Diagnosis	
Normal	21	Normal	21
		Testicular Abnormality	
Mass arising in or replacing testis	9	Seminoma	4*
		Teratoma	2*
		Seminoma and teratoma	1*
		Chronic inflammation	2*
Abnormal testicular echo pattern and enlarged epididymis	9	Epididymo-orchitis	7 + 2*
Small testis with abnormal echo pattern	2	Infarction	2*
Horizontal lie of testis and enlarged epididymis	1	Torsion	1*
Small testis with normal echo pattern	2	Atrophy	2
		Extratesticular Abnormality	
Enlarged epididymis	39	Epididymitis	38 + 1*
Fluid collection around normal testis	16	Simple hydrocele	15 + 1*
Single or multiple round or oval cysts	13	Epididymal cyst	12
		Spermatocele	1*
Blood surrounding intact testis	4	Scrotal haematoma	4
Mass outside testis	1	Liposarcoma of cord	1*
Thickening of scrotal skin	1	Idiopathic scrotal oedema	1
Bowel gas in scrotum	1	Scrotal hernia	1

* Denotes surgical or histological diagnosis; the rest of the final diagnoses are based on clinical assessment and follow-up.

epididymis are not usually visible in their normal state.

Ultrasound examination may show an alteration in size, echo pattern or reflectivity of the testis and epididymis and may show the presence of fluid collections and overlying soft tissue changes. Clinical examination is often difficult in acute inflammatory conditions of the scrotum but ultrasound examination may easily be carried out and no patient refused to be examined. In acute epididymitis, the ultrasound findings are enlargement of part or whole of the epididymis, swelling of the overlying soft tissues, a normal testis and often an associated hydrocele (Fig. 2). The enlarged epididymis may have a uniformly bright echo pattern or contain areas of low reflectivity. When an associated orchitis is present, there is enlargement of the testis which is of lower reflectivity than normal and shows increased through transmission of sound, seen as acoustic "bright up" posterior to the abnormal testis (Fig. 3).

In acute torsion, in addition to epididymal swelling and a hydrocele, an abnormal position of the testis may be demonstrated. However, further cases of torsion need to be examined in order to establish whether an accurate distinction can be made from acute inflammation.

In the differential diagnosis of the painless scrotal swelling, ultrasound examination demonstrates the nature and origin of the swelling. Fluid collections are easily demonstrated. A hydrocele is seen as an echo-free space and the normal testis is clearly demonstrated (Fig. 4). If there have been previous episodes of infection, there may be swelling of the overlying soft tissues and septa may be

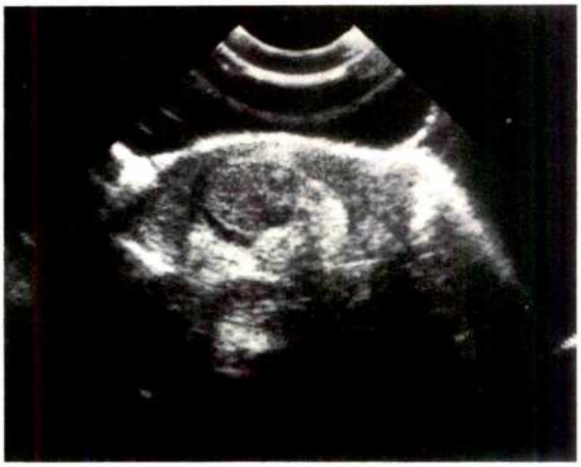

Fig. 2 Acute epididymitis. The epididymis is enlarged and there is swelling of the overlying soft tissues. Longitudinal scan.

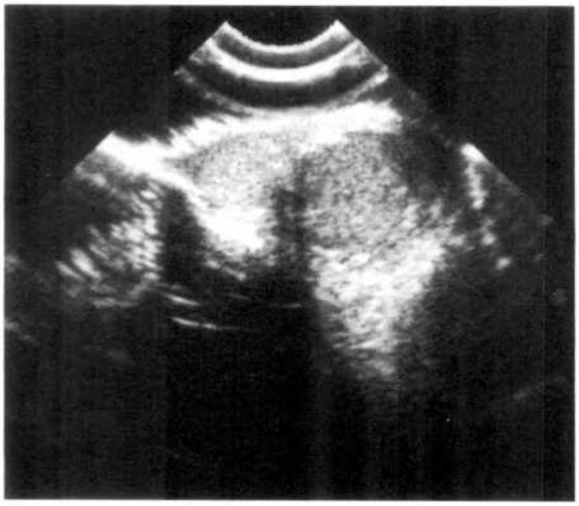

Fig. 3 Acute epididymo-orchitis. There is acoustic enhancement posterior to the enlarged, echo-poor testis. Transverse scan.

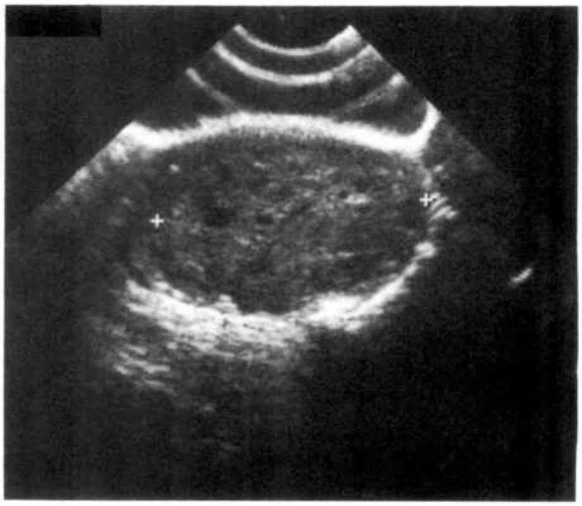

Fig. 5 Testicular tumour, seminoma. The testis has been replaced by a large mass of predominantly low level echoes. Longitudinal scan.

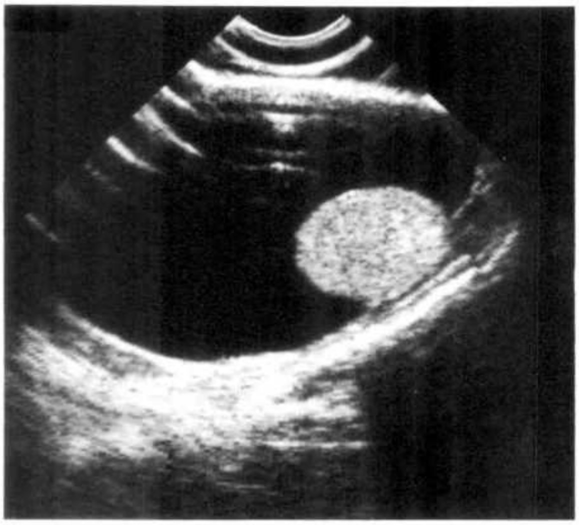

Fig. 4 Hydrocele. The normal testis is clearly visualised. Longitudinal scan.

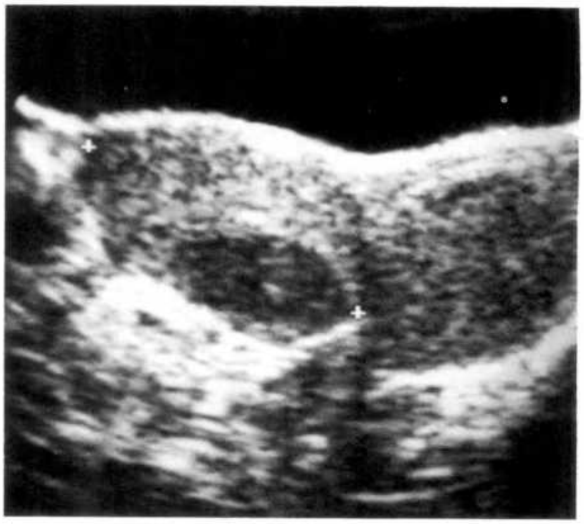

Fig. 6 Testicular tumour, teratoma. There is a mass of low reflectivity measuring 12 mm in length in the lower pole of the right testis. Transverse scan.

seen within the hydroçele. Epididymal cysts are seen as round or oval, echo-free spaces with well defined curved walls. It may be difficult to differentiate between large epididymal cysts and a hydrocele containing septa.

We have examined seven patients with testicular tumours using ultrasound. The demonstration of a testicular tumour depends on the abnormal echo pattern of tumour tissue. This is most commonly of low reflectivity (Fig. 5), but a mixed pattern of high and low reflectivity may be present. Other features that may be seen are an associated hydrocele, echo-free areas due to cystic degeneration and bright echoes with posterior acoustic shadowing due to calcification. Enlargement of the testis may be demonstrated, depending on the size of the tumour. The smallest tumour in our series measured 12 mm (Fig. 6), but lesions as small as 3 to 4 mm in diameter may be detected (Forsberg and Olsson, 1983). It is not possible to differentiate between different histological types of tumour on the basis of the ultrasound features. No testicular tumours were missed on ultrasound examination.

There were two false positive results (Table). The clinical diagnosis was not certain and, in both cases, ultrasound examination showed a solid scrotal mass and no normal testis (Fig. 7). Testicular tumour was diagnosed. Histological examination of the orchiectomy specimens showed fibrotic testes surrounded by chronic inflammatory tissue.

We have seen one case of an extratesticular neoplasm where ultrasound was helpful in making the diagnosis. On clinical examination of the large scrotal swelling, a normal testis could not be palpated. Serological tests for syphilis were positive. Clinical diagnoses including a gumma and testicular tumour. Ultrasound examination showed a normal testis displaced inferiorly by a lobulated mass of predominantly low reflectivity (Fig. 8) and an extratesticular tumour was diagnosed. These findings were confirmed at orchiectomy and the final histological diagnosis was a well differentiated liposarcoma.

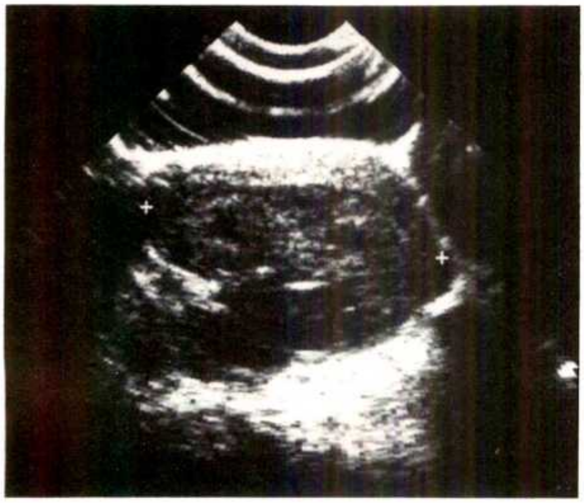

Fig. 7 Chronic inflammation. There is a mass of heterogeneous echo pattern and no normal testis can be visualised. Longitudinal scan.

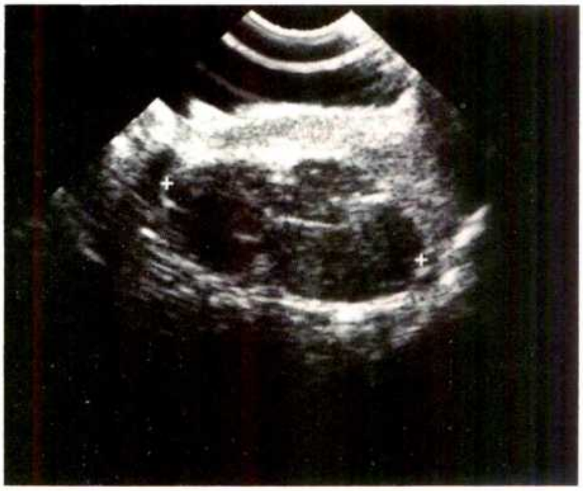

Fig. 8 Extratesticular tumour, liposarcoma. The normal testis is displaced inferiorly by a lobulated mass of low level echoes. Longitudinal scan.

In cases of scrotal trauma, ultrasound examination has demonstrated scrotal haematoma and the state of the underlying testis. In the cases we have seen, the testis has been shown to be intact and no surgical exploration was necessary.

Two cases of testicular infarction were diagnosed on ultrasound. In both cases the testis appeared small and of low reflectivity and there was some associated epididymal enlargement. The clinical diagnosis was in doubt but histological examination confirmed infarction.

Discussion

Ultrasound examination of the scrotum is a rapid, pain-free procedure and diagnostic scans can be obtained using modern general purpose real time sector scanners which are now available in most X-ray departments.

In acute inflammatory conditions, where pain makes accurate clinical examination difficult, ultrasound examination is useful in demonstrating the state of the underlying testis and epididymis. In the difficult scrotal swelling, where the testis cannot be palpated satisfactorily, ultrasound examination demonstrates with a high degree of accuracy whether the origin of the swelling is testicular or extratesticular, and the fluid or solid nature of the swelling. Although we have had two false positive diagnoses of tumour, there have been no false negative diagnoses.

Acknowledgement

We thank Miss Diane Brisley for typing the manuscript

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The Authors

M J. Michell, FRCR, Senior Registrar in Radiology
P. M. Thompson, FRCS, Senior Registrar in Urology
A. J. Yates Bell, FRCS, Consultant Urologist.
J. P. Pryor, MS, FRCS, Consultant Urologist
D A Packham, FRCS, Consultant Urologist.

Requests for reprints to: M. J Michell, Department of Radiology, King's College Hospital, Denmark Hill, London SE5 9ZS.

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AUTHORS' FOLLOW-UP

Frusemide Intravenous Urography in the Diagnosis of Pelviureteric Junction Obstruction

H. N. WHITFIELD, K. E. BRITTON, W. F. HENDRY and J. E. A. WICKHAM

Departments of Urology and Nuclear Medicine, St Bartholomew's Hospital, London

In the original report (Whitfield *et al.*, 1979) a frusemide intravenous urogram (FIVU) was recommended in the diagnosis of pelviureteric junction (PUJ) obstruction. Twenty minutes after an intravenous injection of twice the usual dose of contrast, 40 mg frusemide were given. The size of the renal pelvis 20 min after administration of the contrast and 15 min after the diuretic was measured and compared. Three separate groups were described:

(i) Obstructed—the size of the renal pelvis increased by more than 22%.

(ii) Unobstructed—the size of the renal pelvis increased by less than 10% or contrast was washed out of the collecting system.

(iii) Equivocal—the increase in size of the renal pelvis was between 10 and 20%.

The FIVU has now become an accepted modification of the standard IVU in this hospital, and on receipt of a request for a FIVU the same protocol is automatically put into operation as was described in the original report. However, the computerised measurement of the size of the renal pelvis is not made since, as originally reported, the division between the three groups can readily be made by eye.

When a diagnosis of PUJ obstruction is suspected clinically a FIVU is requested. When a dilated pelvicaliceal system is seen on a standard IVU we would be reluctant to accept a diagnosis of PUJ obstruction without a FIVU. This diagnostic policy has been accepted by our nephrological colleagues. Our radiological colleagues are equally convinced and will, as a matter of routine during a standard IVU, administer an intravenous dose of frusemide if the early IVU films are suggestive of a PUJ obstruction.

We remain firm advocates of the FIVU in the diagnosis of PUJ obstruction and would be unwilling, in the vast majority of patients, to accept the diagnosis without it. Gamma camera studies are still used routinely and the correlation between the two investigations remains in the region of 85%. Both investigations are also employed postoperatively as a matter of routine.

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Requests for reprints to. H. N. Whitfield, Department of Urology, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE

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AUTHORS' FOLLOW-UP

The Intravenous Urodynamogram

R. T. TURNER-WARWICK, C. G. WHITESIDE, E. J. G. MILROY, A. W. PENGELLY and D. T. THOMPSON

Department of Urology, Battle Hospital, Reading

The intravenous urodynamogram (IVUD) was first described by Turner-Warwick *et al.* in 1979. It is a modification of the standard IVU in which upper tract films are kept to a minimum, lower tract films are delayed until the bladder is full (with diuretic expedition if appropriate) and the patient feels the need to void, the patient voids into a urinary flow meter and the record of this forms an integral part of the report, and the post-micturition film is taken without delay.

It thus eliminates the common inaccuracies that arise from an inability to void efficiently unless the bladder is full, and provides an accurate assessment of bladder capacity, urinary flow rate and post-micturition residue.

It is a useful screening test for patients with lower tract symptoms.

The original report from the Middlesex Hospital, where the test is now the routine basic urographic procedure, suggested that the urodynamogram was particularly useful as a preliminary screening test in referral centres. Since 1980 the IVUD has also been used in the district general hospitals of Reading, where it is now the routine screening test for patients with lower tract symptoms. It has proved particularly useful in distinguishing patients in need of prostatectomy from those who require more detailed urodynamic investigation (Turner-Warwick and Whiteside, 1979).

The urodynamogram is one of many ways in which the "standard" IVU may be modified in order to provide economic and accurate answers to specific urological questions, but accurate answers can be given only to accurate questions and the exact purpose of any X-ray must be clearly understood by both the clinician and the radiologist. As described in the original report (Turner-Warwick *et al.*, 1979), this understanding can be greatly increased by including a section headed "Why?" on the request form for any X-ray. Four years ago this small change was made throughout West Berkshire and there is now no doubt, especially amongst radiologists, that it helps clinicians of all specialities to think clearly.

In summary, therefore, 5 years after the report was published the modifications it described have all become routine procedures, not only in teaching hospital practice but also in the district general hospital.

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Requests for reprints to: A W. Pengelly, Department of Urology, Battle Hospital, Oxford Road, Reading, Berkshire

British Journal of Urology (1985), **57**, 353-362

Case Reports

Ureteric Obstruction Secondary to Appendicular Abscess Treated by Trans-uretero-ureterostomy

J. I. HARTY, *Section of Urology, Department of Surgery, University of Louisville School of Medicine, Louisville, USA*

A patient with a right lower quadrant mass and hydronephrosis is described. At exploration the mass proved to be a chronic appendicular abscess which involved the ureter. The patient was managed by appendicectomy and transuretero-ureterostomy. The management of ureteric obstruction secondary to appendicular abscess is briefly discussed.

Case Report

A 12-year-old girl was admitted with cramping abdominal pain and rectal bleeding. The pain resolved and investigation of the rectal bleeding was negative.

Six weeks later the patient presented with an episode of gross haematuria. Abdominal examination revealed a right lower quadrant mass and right ureteric obstruction was seen on the intravenous urogram (Fig.). A ureteric catheter could not be advanced beyond the point of obstruction.

Through a midline exploratory laparotomy an inflammatory mass of large and small bowel was found, but there was no free pus. A necrotic appendix was removed and an attempted ureterolysis was unsuccessful owing to extreme periureteric fibrosis. The ureter was divided above the pelvic brim and a transuretero-ureterostomy performed. Intravenous urography 2 months post-operatively was normal.

Comment

Ureteric obstruction secondary to appendicular abscess rarely requires surgical intervention since most cases resolve following appendicectomy and drainage of the abscess (Cook, 1969). However, occasionally relief of ureteric obstruction has required ureterolysis or ureteroneocystostomy (Carroll and Laughton, 1973; Richie *et al.*, 1975). This is the first reported case in which transuretero-ureterostomy was used to manage a ureter obstructed by an appendicular abscess.

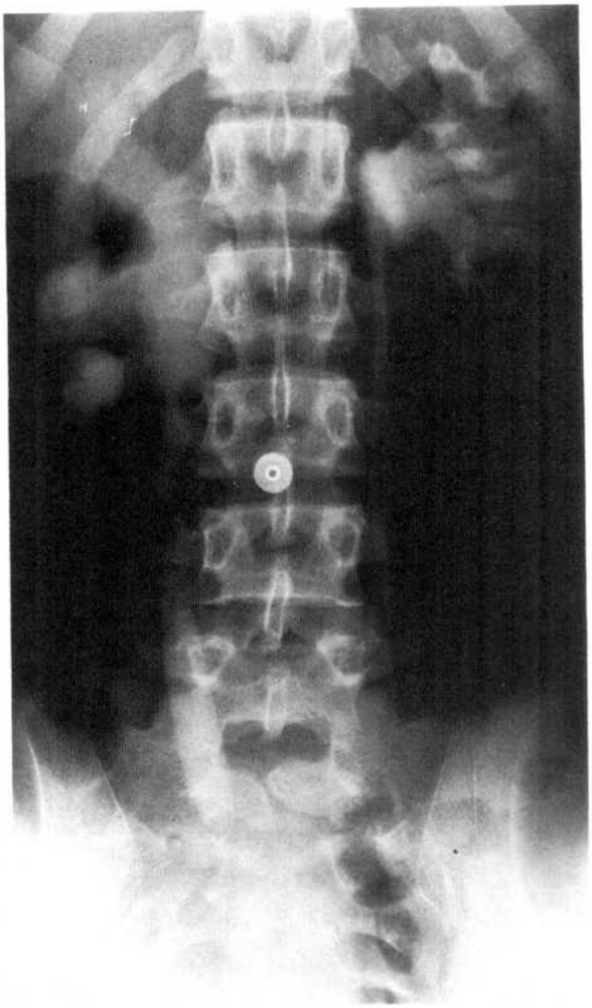

Fig. IVU showing right ureteric obstruction at the pelvic brim.

The factors which led to this procedure were:

(1) A ureteric catheter could not be passed beyond the obstruction.
(2) Gross haematuria suggested severe ureteric involvement.
(3) Ureterolysis was extremely difficult owing to the amount of periureteric fibrosis.
(4) Psoas hitch and ureteroneocystostomy through an infected area was contra-indicated.
(5) The uretero-ureterostomy anastomosis could be performed in a clean area away from the abscess.
(6) The midline incision allowed excellent exposure for a transuretero-ureterostomy.

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Requests for reprints to: J. I. Harty, Department of Surgery, University of Louisville School of Medicine, Ambulatory Care Building, Louisville, Kentucky 40292, USA.

Percutaneous Pyelolysis: a New Approach to Post-transplant Ureteric Obstruction

H. J. E. LEWI, I. McMILLAN, S. BRAMWELL and K. F. KYLE,
Department of Urology, Western Infirmary, Glasgow

Ureteric complications following renal transplantation remain a significant cause of morbidity and graft failure (Mundy *et al.*, 1981). In ureteric obstruction, ureteropyelostomy involving anastomosis of the recipient ureter to the donor pelvis has been used (Glass *et al.*, 1982). Despite the low morbidity rate associated with this procedure, late stenosis at the pelviureteric anastomosis may occur.

Percutaneous pyelolysis has been suggested as an alternative to surgical treatment in patients with pelviureteric obstruction (Whitfield *et al.*, 1983; Wickham and Miller, 1983).

We report a case of pelviureteric obstruction in a renal transplant recipient treated by percutaneous pyelolysis.

Case Report

A 51-year-old female on haemodialysis for renal failure received a left cadaver renal transplant in November 1983. Immunosuppression was maintained by prednisolone and azathioprine, and the renal allograft functioned within 24 h. The post-operative course remained uneventful and she was discharged at 2 weeks with a creatinine clearance of 71 ml/min.

In January 1984 she presented with ureteric obstruction, hydronephrosis and deteriorating renal function. At operation the ureterovesical anastomosis was fibrotic and stenosed and reimplantation of the ureter was subsequently performed. Post-operatively there was persistent leakage of urine through the wound and a further exploration was performed. Because of fibrosis of the donor ureter, a ureteropyelostomy was fashioned and the recipient left ureter was anastomosed to the donor renal pelvis.

Despite splinting of the anastomosis, urine leakage and periureteric fibrosis ensued. To prevent progressive deterioriation of renal function, an open nephrostomy was performed and the kidney was drained by a 20F Malecot catheter. After 6 weeks' drainage, the creatinine clearance had improved to 40 ml/min and an antegrade pyelogram showed obstruction of contrast flow at the pelviureteric anastomosis. At this time all urine was being produced via the nephrostomy tube and attempts at clamping the tube to encourage flow via the ureter persistently failed.

Percutaneous pyelolysis was carried out in the manner described by Wickham and Miller (1983) and Whitfield *et al.* (1983). Under a general anaesthetic the nephrostomy tube was removed and the track dilated to 36F using graded teflon dilators. A 34F nephroscopy cannula was inserted into the track, through which a rigid-end viewing urethroscope with a fine-bladed urethrotomy knife was passed. The strictured pelviureteric junction

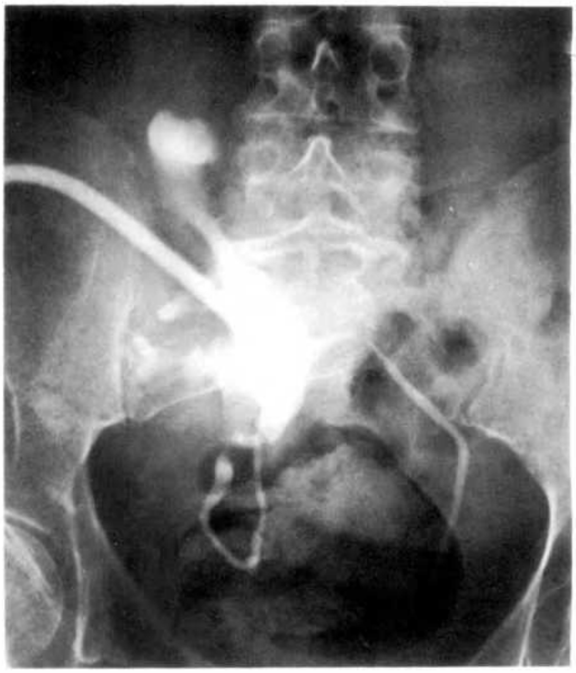

Fig. Antegrade pyelogram 7 days after percutaneous pyelolysis shows good flow of contrast from the transplant kidney via the recipient left ureter into the bladder.

was visualised and divided along its anterolateral border. Temporary drainage was obtained by reinsertion of a nephrostomy tube, through which an antegrade pyelogram was obtained on day 7. This demonstrated a free flow of contrast down the ureter into the bladder and allowed removal of the nephrostomy tube (Fig.). The nephrostomy track was completely dry by 72 h and all urine was passed via the bladder.

Follow-up 6 weeks later demonstrated normal urinary flow with no evidence of urine leak and moderately good renal function with a creatinine clearance of 40 ml/min. At 6 months normal urinary flow continues and the patient's renal function has continued to improve with a creatinine clearance of 52 ml/min.

Comment

Ureteric complications following renal transplantation occur in up to 14% of patients and account for a significant number of cases of renal allograft dysfunction and loss (Mundy *et al.*, 1981). Management of post-transplant ureteric obstruction varies and includes both long-term nephrostomy drainage and ureteric reconstruction (Goldstein *et al.*, 1981; Glass *et al.*, 1982). In a number of cases treatment failure leads to loss of the transplant kidney. In our patient, obstruction was treated by ureteropyelostomy. Late obstruction due to stenosis at the pelviureteric anastomosis led to progressive deterioration in renal function which was managed at first by nephrostomy drainage and later by percutaneous pyelolysis.

Percutaneous pyelolysis is a simple, safe and effective procedure for treatment of post-transplant pelviureteric obstruction.

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Requests for reprints to: H. J. E. Lewi, Department of Urology, Western Infirmary, Glasgow G11 6NT.

Polyarteritis Nodosa: an Unrecognised Cause of Fournier's Gangrene

R. DOWNING and J. BLACK, *Department of Surgery, Royal Infirmary, Worcester*

A local predisposing cause is frequently identified in Fournier's gangrene, but a systemic aetiology is rare. We therefore present a case of Fournier's gangrene occurring in association with polyarteritis nodosa.

Case Report

A 69-year-old man with a history of angina pectoris experienced central chest pain and breathlessness followed by lower abdominal pain and scrotal gangrene. He was pyrexial (38°C), dehydrated, and the necrotic scrotum was typical of Fournier's gangrene (Fig.). He was treated with intravenous fluids and antibiotics. Investigation revealed a neutrophil leucocytosis ($17.1 \times 10^9/l$); ESR 65 mm; serum urea 24.8 mmol/l and creatinine 187 μmol/l; serum albumin 21 g/l. Serum globulins, liver function tests and chest X-ray were normal. An ECG showed anterior subendocardial infarction. A scrotal swab grew haemolytic streptococci of Lancefield's group A, but the urine was sterile.

Three days later he developed abdominal tenderness and distension. Intestinal obstruction was diagnosed by

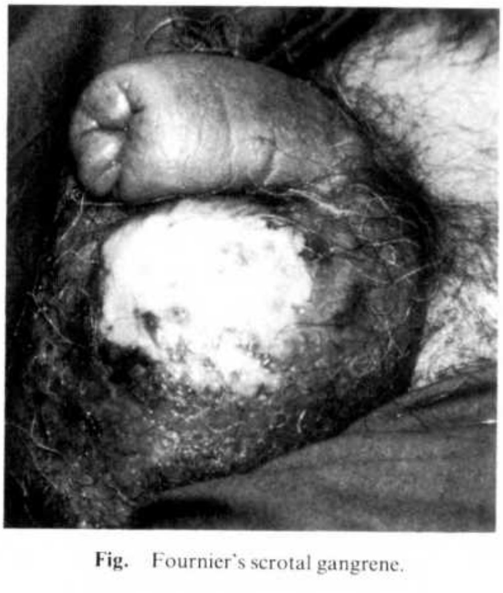

Fig. Fournier's scrotal gangrene.

plain abdominal X-rays but laparotomy revealed a generalised distension of the small and large bowel, with ischaemic areas most marked in the proximal jejunum and ascending colon. All visible mesenteric vessels were pulsatile. The abdomen was closed. Histological examination of a biopsy from the right rectus abdominus muscle showed acute inflammatory changes in connective tissue involving small veins. Arteries in the specimen were normal. Further investigations revealed that he was strongly sero-positive for vascular smooth muscle antibodies (rat kidney); he was sero-negative for hepatitis B surface antigen and antibody; ANF was negative and serum electrophoresis normal. The underlying aetiology was considered to be polyarteritis nodosa and he was treated with prednisolone, azathioprine, heparin and intravenous Dextran-40, and in 5 days his chest pain and ileus had resolved. The scrotum was debrided and healed by second intention. He is now maintained on azathioprine only. Renal function remains impaired (urea 19.3 mmol/l; creatinine 202 μmol/l).

Comment

The diagnosis of polyarteritis nodosa is most commonly based on the finding of a multisystem disorder which in our patient included myocardial infarction, acute intestinal ischaemia and impairment of renal function. Laboratory investigations are of limited value. A positive muscle biopsy and hepatitis B antigenaemia are found in less than 50% of cases (Maxeiner *et al.*, 1952; Zuckerman, 1976) and their absence did not preclude the diagnosis. Furthermore, the identification of vascular smooth muscle antibodies was indicative of a vasculitis.

Fournier's gangrene may be accompanied by a paralytic ileus for which no adequate explanation has been reported (Rudolf *et al.*, 1975). In such cases we suggest that polyarteritis nodosa should be considered a possible aetiology.

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Requests for reprints to: R. Downing, Department of Surgery, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH.

Papillary Cystadenoma of the Epididymis

H. K. GREKA, A. R. MORLEY and D. EVANS, *Departments of Histopathology and Urology, Freeman Hospital, Newcastle upon Tyne*

Case Report

A 33-year-old married man, without children, had been investigated because of persistent pain in the left inguinal region for 10 years. Excision of a left varicocele 7 years previously had not relieved the pain. There was no relevant family history.

Examination revealed a tender epididymal nodule 0.5 cm in diameter. IVU, MSU and cystoscopy were normal. On exploration a solid nodule with a yellowish surface was excised.

Microscopy showed a capsule and efferent and epididymal tubules, some dilated and containing spermatozoa. The tumour showed acinar spaces, colloid, columnar lining cells with clear cytoplasm (Fig. 1). The nuclei had prominent nucleoli. In some acini the epithelium formed papillary excrescences. The cytoplasm was PAS-negative but stained for fat. A diagnosis of papillary cystadenoma of the epididymis was made.

Electron microscopy showed vacuolated cytoplasm with irregular apical microvilli. The cilia were confined to the cells of the efferent ducts (Fig. 2). Intra-cytoplasmic granules were found occasionally in tumour cells and between the tubules were macrophages bearing dense material.

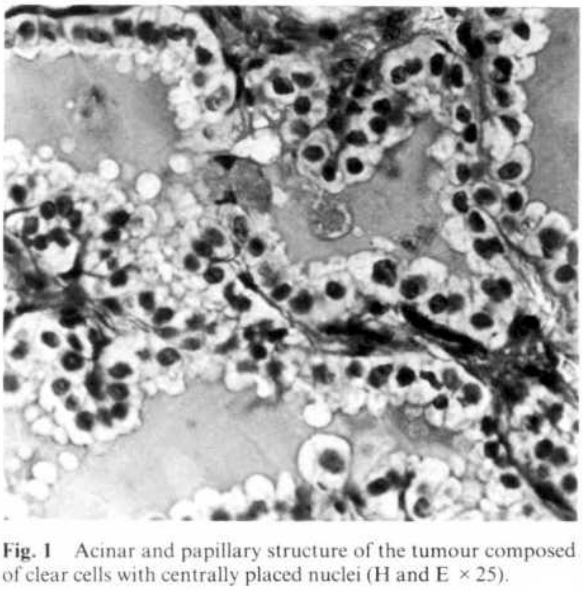

Fig. 1 Acinar and papillary structure of the tumour composed of clear cells with centrally placed nuclei (H and E × 25).

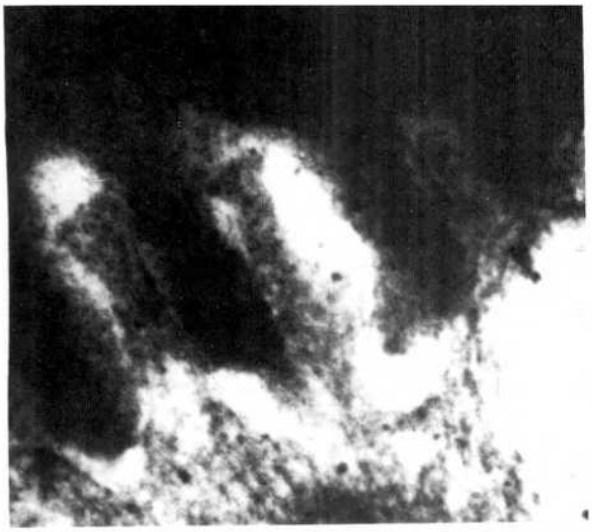

Fig. 2 Microvilli on the apical surface of the tumour cell (× 30,000).

Comment

Sherrick (1956) suggested that cystadenomas originated from spermatoceles but Tsuda *et al.* (1976) showed that the tumour originated in the efferent ducts. A spermatocele is not now considered a prerequisite for formation of a tumour.

The efferent ducts are lined by an epithelium containing ciliated cells, whereas the ductus epididymis cells possess elongated microvilli (stereocilia). Easton and Claridge (1964) demonstrated ciliated cells in papillary cystadenomas. The ultrastructural study of Tsuda *et al.* (1976) demonstrated long microvilli, as in our case.

Our patient had no features of Lindau's disease, CNS vascular tumours, or hamartomas of the pancreas and kidney as described by Melmon and Rosen (1964) in association with papillary cystadenoma of the epididymis.

Acknowledgement

We acknowledge the assistance and encouragement given by Mr R. R. Hall.

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Requests for reprints to: A. R. Morley, Department of Laboratory Medicine, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

Adenocarcinoma Occurring Within a Caecocystoplasty

R. S. KIRBY and R. W. LLOYD-DAVIES, *Department of Urology, St Thomas' Hospital, London*

Case Report

A 42-year-old patient presented with a vesicovaginal fistula following a Wertheim's hysterectomy and external radiotherapy for squamous cell carcinoma of the cervix. Formal closure was unsuccessful and in view of her low capacity bladder a caecocystoplasty was performed. This functioned well for a considerable time but a bout of septicaemia with bilateral upper tract dilatation made further surgery necessary. Urinary diversion was undertaken by means of a jejunal conduit, the caecocystoplasty remnant being left *in situ*. Eight years later the patient developed recurrent urethral discharge. The caecocystoplasty was removed and histological examination confirmed the presence of adenocarcinoma of the colon (Fig.). The patient made a satisfactory recovery and remains disease-free 2 years later.

Comment

This is the first report of a colonic adenocarcinoma occurring within a caecocystoplasty. There is a well established increase in the risk of colonic carcinoma in patients who have undergone uretero-

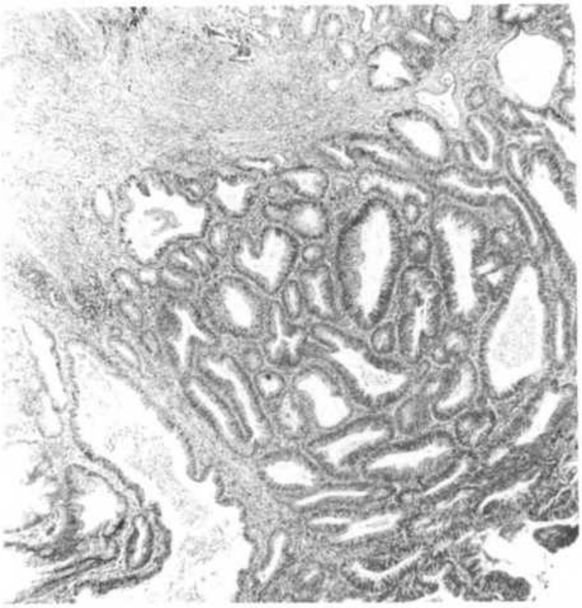

Fig. Section showing adenocarcinoma (H and E × 7).

sigmoidostomy (estimated as 500 times greater than in the normal population (Urdaneta *et al.*, 1966)). A direct carcinogenic effect resulting from the combination of urinary and faecal streams has been postulated, and nitrosamines implicated. Recently, however, a case of carcinoma occurring in a colonic conduit isolated from the faecal stream has been reported (Chiang *et al.*, 1982). In our case the caecal mucosa was exposed solely to urine flow for a period of 1 year. The case suggests that urinary constituents may exert a carcinogenic effect on colonic mucosa, even in the absence of a faecal stream. Since there is a considerable time-lag in the development of malignant change at a ureterocolic anastomosis (average 21.4 years (Leadbetter *et al.*, 1979)), there exists a worrying possibility that we may see further malignancy within caecocystoplasties in the future.

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Requests for reprints to: R. S. Kirby, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

Penile Carcinoma in the First Decade of Life

K. L. NARASIMHARAO, H. CHATTERJEE and A. J. VELIATH, *Departments of Paediatric Surgery and Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India*

Case Report

A 9-year-old, uncircumcised Hindu child was admitted with swelling of the penis of 7 months' duration. The swelling had started in the glans and progressively increased in size. Initially it had been painless but a purulent discharge developed and it became painful, with burning micturition. There was no history of trauma or sexual abuse. The distal half of the penis and glans were replaced by an infected, foul-smelling fungating growth measuring 2 × 2 × 2.5 cm and firm in consistency. About 2 cm of the proximal penile shaft were free. Insignificant lymph nodes were palpable over the left inguinal region. Serological tests for syphilis, filarial skin test and Donovan bodies on smear were negative. A wedge biopsy revealed the lesion to be a squamous cell carcinoma (Fig.) and partial amputation of the penis was carried out. The resection line was tumour-free on histological examination and inguinal lymphadenitis subsided with antibiotic therapy. The patient is disease-free 3 years after surgery.

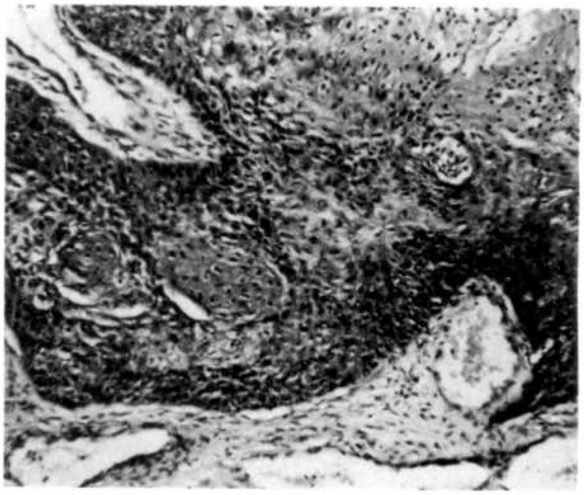

Fig. Malignant squamous cells with hyperchromatic nuclei and keratin pearl formation. (H and E × 100).

Comment

Carcinoma of the penis in the first decade of life has been reported on only three previous occasions (Creiti, 1944; Kini, 1944; Rai, 1959) but documentation has been poor. The likelihood of misdiagnosing these cases as a granulomatous lesion is high without a biopsy. It is significant that three of four reported patients, including ours, lived in the same geographical area where penile carcinoma is very common. Poor local hygiene resulting from either ignorance or lack of privacy in domestic life is responsible for the high incidence of penile carcinoma, particularly at an early age.

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Requests for reprints to: K. L. Narasimharao, Department of Paediatric Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh-160 012, India.

Foreign Body Urethral Calculus 9 Years after Traumatic Perforation of the Rectum

S. AHMED and L. MORRIS, *Departments of Urology and Radiology, Adelaide Children's Hospital, North Adelaide, Australia.*

Case Report

D.S., a 4-year-old boy, sustained an anterior rectal perforation when he fell astride a sharp object (Fig. 1). This was successfully managed by performing a defunctioning colostomy which was closed 3 months later.

At the age of 13 years the boy presented with an acute urinary tract infection. A tender lump was palpable over the mid-urethra. Investigations showed a urethral calculus which, surprisingly, had been missed on initial evaluation (Fig. 2).

A urethrotomy was performed for removal of the stone but it slipped into the bladder and was removed via a small suprapubic cystotomy.

The stone was 12 × 7 × 4 mm, with an outer crystalline layer and a nucleus of fibrous mesh which proved to be polyester fibre.

Retrospectively, there was no history of urinary problems at the time of rectal injury. A hole had, however, been noticed in the boy's pants and a piece of clothing had presumably been implanted in the paraurethral region.

Comment

Urethral calculi may develop primarily in the urethra but the majority are migratory in that they originate in the bladder or upper urinary tract (Paulk *et al.*, 1976). Primary urethral calculi usually form in association with chronic urinary tract infection or in patients with urethral abnormalities such as diverticula or strictures (Marya *et al.*, 1977). Our case was unique in that the calculus developed around a foreign body which had presumably been implanted in the paraurethral region at the time of the rectal perforation.

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Requests for reprints to: S. Ahmed, Department of Paediatric Urology, Adelaide Children's Hospital, North Adelaide, South Australia 5006.

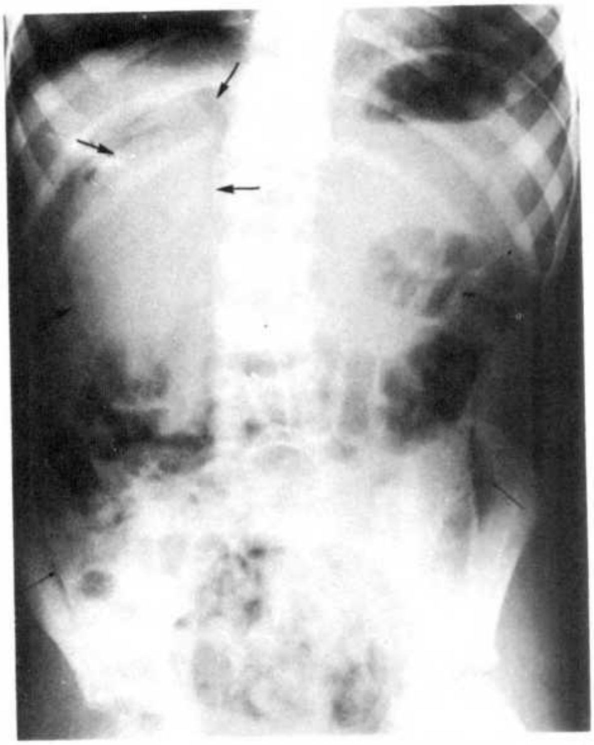

Fig. 1 Extraperitoneal air was noted in both flanks and around the right kidney (arrows), indicating that the impaling injury had caused a rectal perforation.

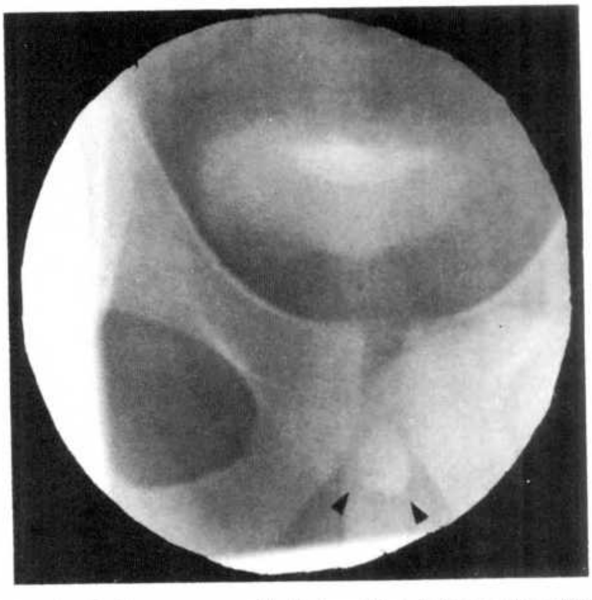

Fig. 2 Radio-opaque urethral stone lying between the pubic bones; micturating cystourethrogram showing anterior urethral deformity due to the impacted calculus.

Bilateral Severe Hydroureteronephrosis due to Uterine Prolapse

L. KONTOGEORGOS, P. VASSILOPOULOS and A. TENTES, *Department of Urology, Athens Naval Hospital, Athens, Greece*

A case of uterine prolapse accompanied by severe bilateral hydroureter and hydronephrosis and treated by the "le Fort" conservative operation is described.

Uterine prolapse is usually found in the multiparous and elderly but urological complications are uncommon. Hydronephrosis is one of the most serious complications and if untreated may lead to renal insufficiency.

Case Report

S.M., aged 76 years, para II, was admitted to hospital with urinary retention. She had been suffering from uterine prolapse for several years.

Her general condition was fair. Clinical examination revealed no abnormality apart from third degree uterine prolapse. Blood pressure was 125/90 mm Hg. Laboratory investigation revealed pyuria due to *Escherichia coli* and slight anaemia (Hb 11.5 g/dl). Blood urea and creatinine were normal.

An intravenous urogram showed poor visualisation of both kidneys due to the hydronephrotic changes, especially on the right side. A subsequent infusion urogram with films after 1 h revealed marked stasis in the kidneys and ureters, which terminated below the symphysis pubis (Figs 1 and 2). In view of the patient's age and general condition conservative surgery under local anaesthesia was thought advisable and the "le Fort" operation followed by high posterior colporrhaphy was carried out.

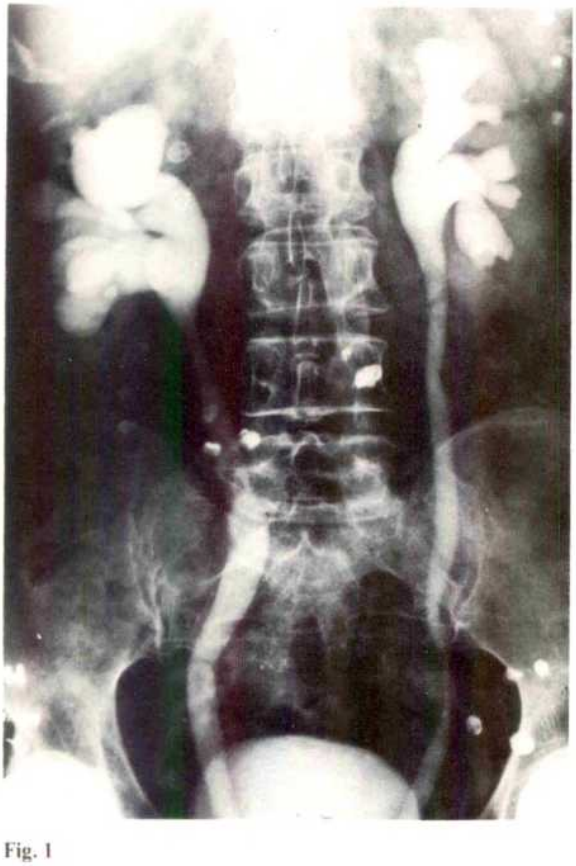

Fig. 1

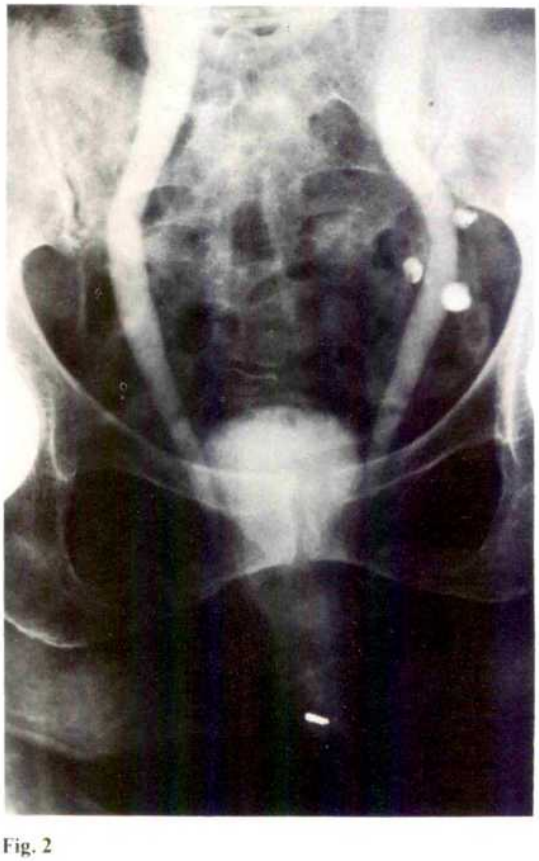

Fig. 2

The patient made an uneventful recovery and an intravenous urogram 1 month later was normal.

Comment

The incidence of hydronephrosis in women with procidentia is between 4 and 7% (Stochli and Hochbule, 1959; Rubin *et al.*, 1974; Persky *et al.*, 1978) and is due to ureteric obstruction. This may be caused by kinking or intramural stretching of the ureters, but is most likely due to compression of the ureters by the uterine vessels which form a vascular plexus around the distal ureters.

The symptoms of procidentia are related either to the genital system or to the upper urinary tract.

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Requests for reprints to: L. Kontogeorgos, 8 Herodotou Street, Athens 139, Greece.

Amputation of the Penis. A Useful Appliance to Assist Micturition

V. P. O'MALLEY, *Department of Surgery, Princess Margaret Hospital, Swindon*

Case Report

A.E., a 61-year-old engineer, presented in April 1971 with a 4-week history of an ulcerating lesion of his penis. Past medical history showed nothing relevant and no history of venereal disease. Physical examination revealed a healthy male in no distress. Cardiovascular and respiratory systems were normal. Abdominal examination was normal. Examination of his genitalia revealed a 2-cm ulcer on the glans beneath the foreskin. No inguinal lymphadenopathy was found. Chest and abdominal X-rays were normal. Biopsy of the lesion confirmed the clinical suspicion of infiltrating carcinoma and he underwent subtotal amputation of the penis. Subsequent follow-up showed no evidence of recurrence and he was well when last seen in May 1980. Because of his disability when attempting micturition he developed his own device to help him micturate, standing up, with accurate direction of the urinary stream. He turned the device in stainless steel on his lathe at work. This consisted of a funnel-like appliance (Figs 1 and 2) which when applied allowed him to micturate virtually normally. After use, he would simply walk to the washhand basin, rinse it and dry it and slip it into his pocket.

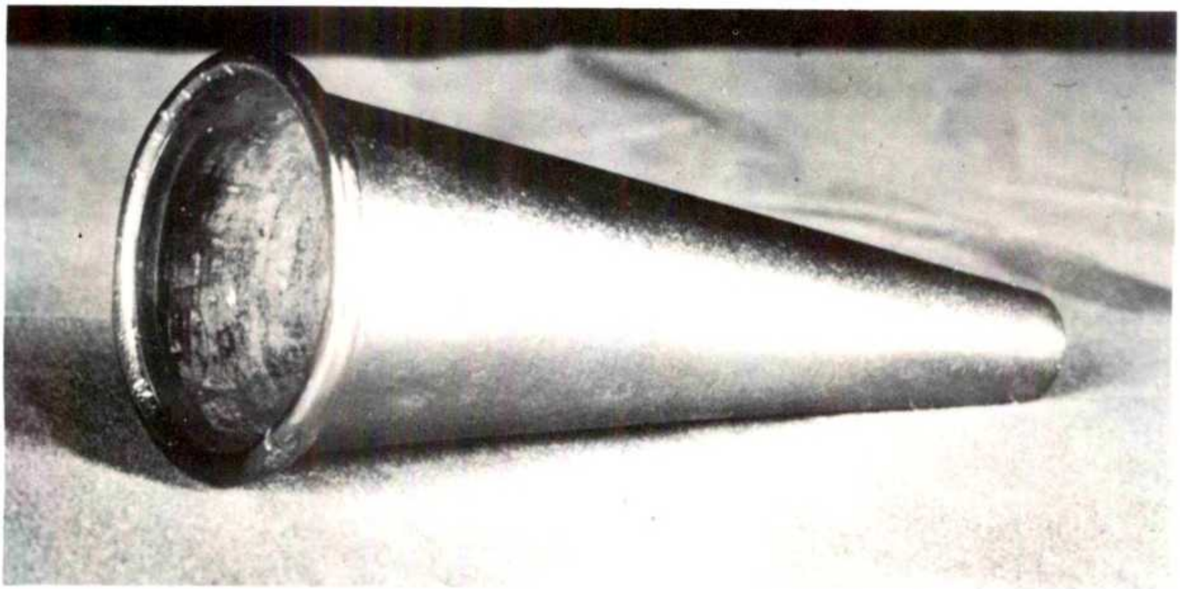

Fig. 1 The apparatus.

Comment

Subtotal amputation is often necessary for carcinoma of the penis (Khezri *et al.*, 1978) and the absence of the penis produces tremendous psychological trauma in addition to the inability to micturate in a controlled manner (Sawhney, 1967). The penile stump or remnant is often distressing to the patient due to frequent soiling and dribbling because he must sit instead of stand to micturate. This report illustrates how necessity is, indeed, the mother of invention and shows how one patient developed his own apparatus to cope with his problem and enabled him to micturate in a reasonable fashion without embarrassment. We have since recommended this type of device to two other patients with very gratifying results.

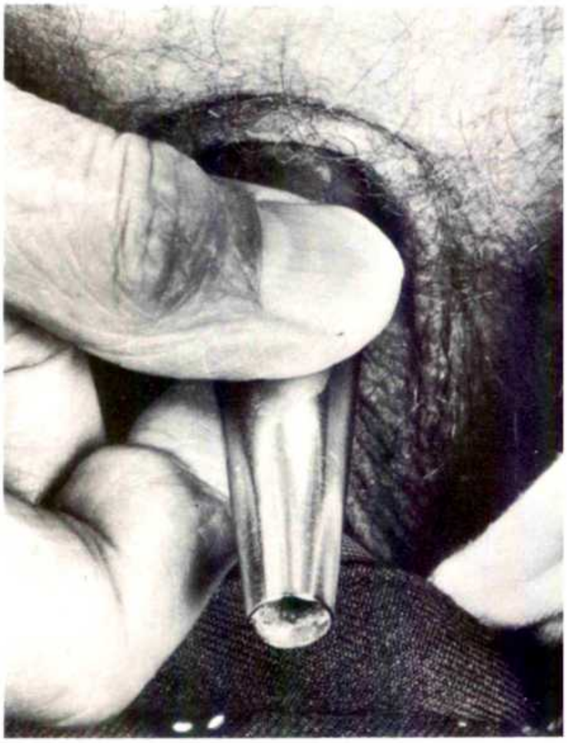

Fig. 2 The apparatus in use.

Acknowledgements

The author thanks Mr P. Powley for permission to prepare this report and the Photographic Department, Princess Margaret Hospital, Swindon, for the photographs.

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Requests for reprints to: V. P. O'Malley, 8 Waterside, Galway, Irish Republic.

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Notices

British Association of Urological Surgeons

President: Professor J. P. Blandy, DM, MCh, FRCS, FACS

Annual Meeting: Eastbourne, 9-12 July 1985

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Edinburgh Urological Festival

Edinburgh. 28-30 August 1985

The Urological Festival is a post-graduate course of lectures by invited speakers and short papers by participants.

The main topics for the 1985 meeting include reconstructive urological surgery, psychosexual medicine, computers in urology, endo-urology and recent advances in chemotherapy.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Urological Research Meeting

Guy's Hospital, London. 10 January 1986

The meeting will provide a forum for the informal presentation and discussion of completed work and work in progress with invited participants from the related basic sciences such as smooth muscle physiology and pharmacology, oncology, anatomy and nephrology.

Further particulars from: Mr A. R. Mundy, Department of Urology, Guy's Hospital Medical School, London Bridge, London SE1 9RT. Please state if you wish to present a paper.

Shackman Travelling Fellowship

The Fellowship for 1985 has been awarded to Mr A. C. Buck, Cardiff, to enable him to work in Munich University on the subject of "The influence of prostaglandins and their inhibitors on calcium transport in the kidney."

Aluminium in Renal Disease

University of Surrey, Guildford. 16-18 September 1985

An international conference to highlight recent knowledge of the problems with aluminium and other metals in the management of renal failure.

Further information from: Mrs Janet Williams, Robens Institute, University of Surrey, Guildford GU2 5XH.

European Nuclear Medicine Congress 1985

London. 3-6 September 1985

Further particulars from: Congress Secretariat, Institute of Nuclear Medicine, Middlesex Hospital, Medical School, Mortimer Street, London W1N 8AA.

12th Meeting of the International Study Group for Steroid Hormones

Rome, Italy. December 1985

The main topics of the meeting will be:

1. Steroid peptide interaction
2. Sex hormone antagonists.
3. Intratissular steroids and hormone dependent corneu.

Deadline for presentation of abstracts: 30th June 1985.

Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma, viale del Policlinico, 00161 Rome, Italy.

Seventh Congress of European Association of Urology

Budapest, Hungary. 26-28 June 1986

Further particulars from: Professor F. Balogh, Department of Urology, Semmelweis University of Medicine, Maria U. 39, 1085 Budapest VIII, Hungary.

British Journal of Urology (1985), **57**, 364

Book Reviews

Bailey and Love's Short Practice of Surgery. Nineteenth edition. Edited by A. J. Harding Rains and H. D. Ritchie. Pp. x + 1301. London: Lewis. 1984. Price £28.00.

This reviewer was aged one when the first edition of Bailey and Love appeared—both book and reviewer have undergone substantial changes since then. In recent years Bailey and Love has acquired specialist contributors but this was inevitable since areas of surgery have progressively become more specialised. Many might now ask what is general surgery but a better question is "What is surgery in general?", *i.e.* the body of knowledge that all surgeons should have whether they are bone setters, lithotomists or gastrointestinal endoscopists. This book still attempts to cover the entire general surgical and specialist field from wound healing to organ transplantation. It remains easy and often fascinating reading and still retains some amazing clinical photographs as well as the one-liner historical notes. It is presumed that this book is mainly for the undergraduate but the style is becoming dated and because it attempts to cover everything the student is likely to seek a smaller text and only pick out selected items from a book such as this. It may even be more profitable to read that selected item in a more contemporary text or journal. Nevertheless this book is a survivor but will it make another 50 years? The book may but this reviewer will not.

Urologic Cancer. A Multidisciplinary Perspective. Edited by M. B. Garnick and J. P. Richie. Pp. xii + 275. New York, London: Plenum Press. 1983. Price $35.00.

This book was prepared from a course on the management of urological cancers held in Boston in 1982. Much of it is written in the form of short notes and this undoubtedly makes it easy to get the message. Although it does not intend to compete with more recent textbooks on urological cancer, it is very comprehensive and up-to-date. It covers each organ site and new work on markers and chemosensitivity as well as the present role of chemotherapy. It is an excellent summary of the subject with a useful list of references after each chapter and is recommended as a refresher course on these cancers.

Infertility in the Male. Edited by L. I. Lipshultz and S. S. Howards. Pp. xii + 409. New York, Edinburgh, London, Melbourne: Churchill Livingstone. 1983. Price £40.00.

This is a well referenced general text about male infertility and represents modern thought. Half of the book is concerned with physiology and half is of direct clinical relevance. There are 22 contributors and some variation in style is inevitable. The diagrams of operative technique are excellent, although one could quibble over some details; for example, the successful pregnancy rate of 20% following epididymovasostomy is almost certainly over-optimistic and takes no account of the primary pathology (post-gonococcal or idiopathic). Unfortunately, our understanding of male infertility is still at an early stage and it is not surprising that the sections of the book which deal with treatment can offer nothing new. It is a pity that there is no chapter on the role of *in vitro* fertilisation for male infertility, since many patients request information from their clinicians on this topic.

This book is recommended for departments with a special interest in male infertility.

Hydrogen Ion Transport in Epithelia. Edited by J. G. Forte, D. G. Warnock and F. C. Rector, Jr. Pp. xxii + 479. Chichester: Wiley. 1984. Price £57.75.

This volume includes papers given at an offshoot of the American Physiological Society in Honolulu in 1983. Emphasis is given to recent developments in our understanding of proton transport and its control in gastric mucosa and renal tubules. Much of the work applies to isolated membrane vesicles. The theoretical basis of our knowledge of renal acidification by metabolic processes, determinants of tissue CO_2 tension, and H^+ and HCO_3^- transport in various tubular locations are discussed. This book will appeal primarily to those who plan the future of urology rather than to the contemporary clinician.

Book Received

Advances in Nephrology. (From the Necker Hospital). Volume 13. Edited by J. P. Grünfeld and M. H. Maxwell. Pp. xxiii + 383. Oxford: Blackwell. 1984. Price £55.00.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

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Study of neuroblastic cells throughout adrenal gland development. (J. P. Barbet *et al.*) *Ann. Pediat.* 1984, **31**, 697.

Isolated unilateral adrenal hemorrhage after motorcycle race. (A. Hubens *et al.*) *J. Trauma*, 1984, **24**, 765.

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KIDNEY

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Scintigraphic evaluation of the urinary system in a case of severe renal trauma. (D. L. Bushnell *et al.*) *J. Nucl. Med.* 1984, **25**, 1053.

Increased renal parenchymal accumulation of Tc-99m HDP in kidney contusion. (Z. Salimi *et al.*) *Clin. Nucl. Med.* 1984, **9**, 574.

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Unilateral nonvisualization of excretory urography after external trauma. (A. S. Cass and M. Luxenberg.) *J. Urol.* 1984, **132**, 225.

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[1] Titles in this issue have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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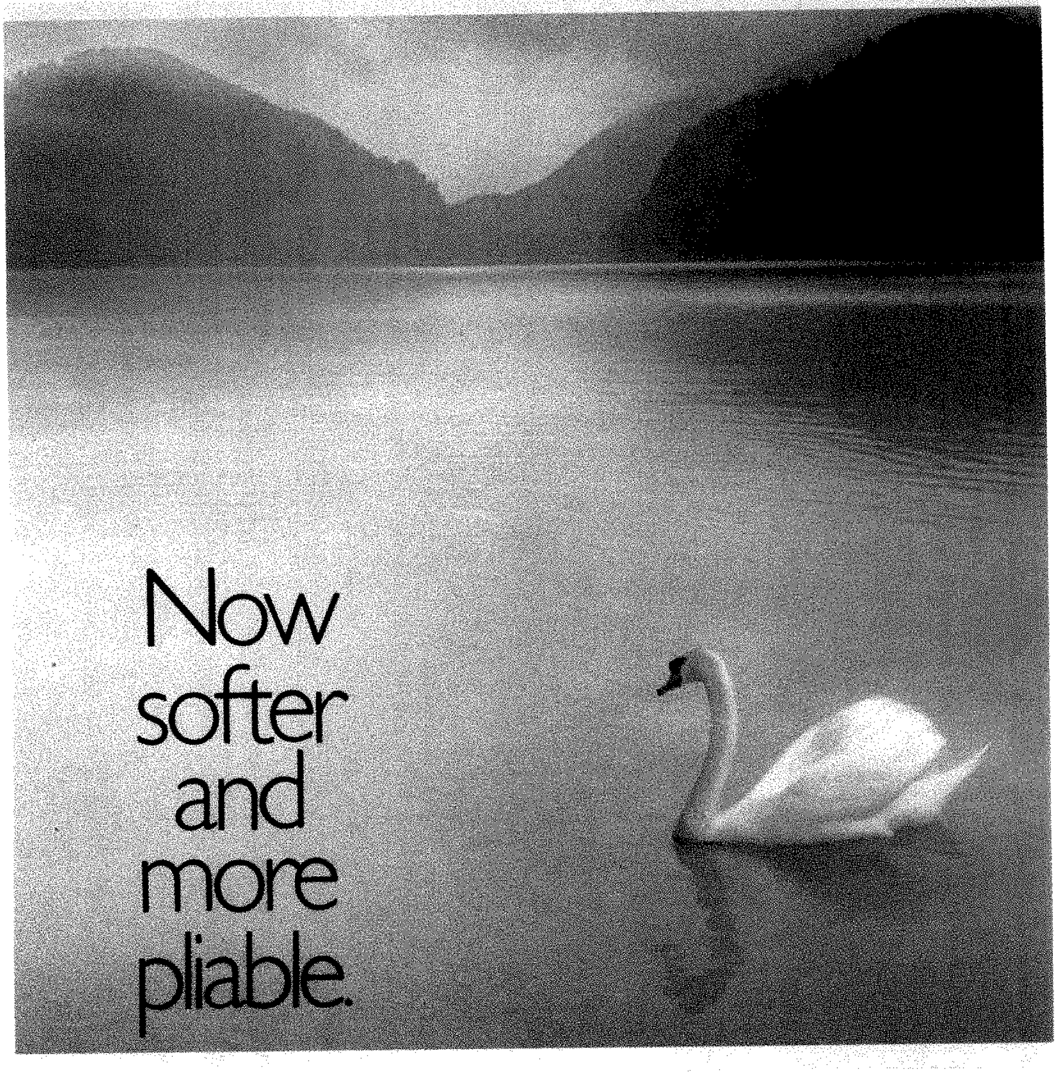

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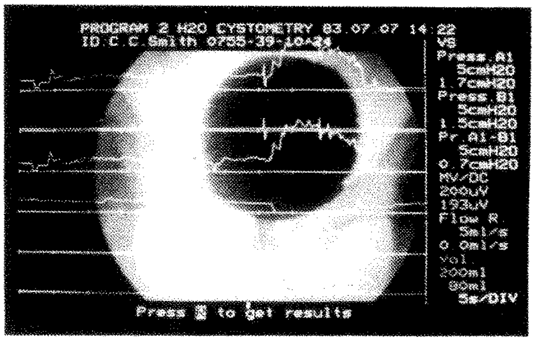

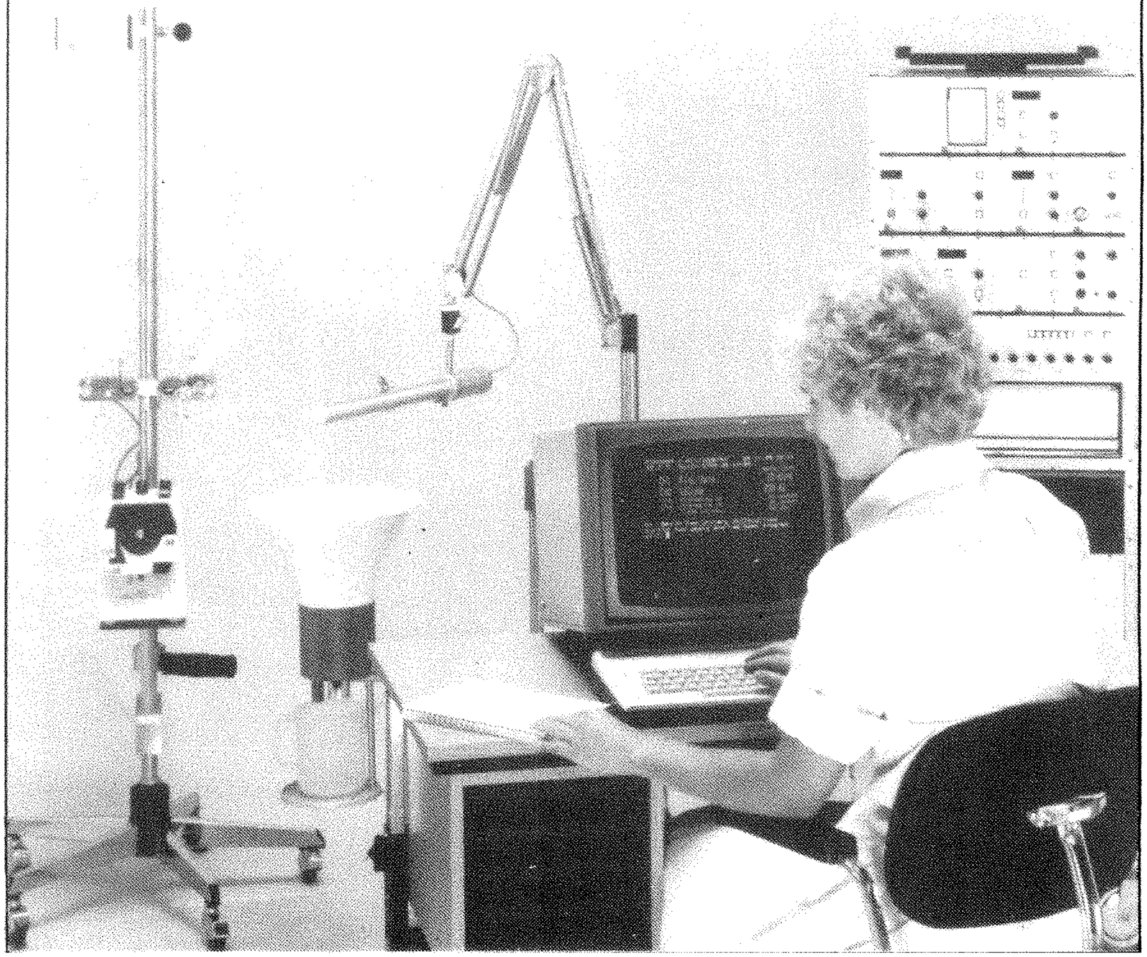

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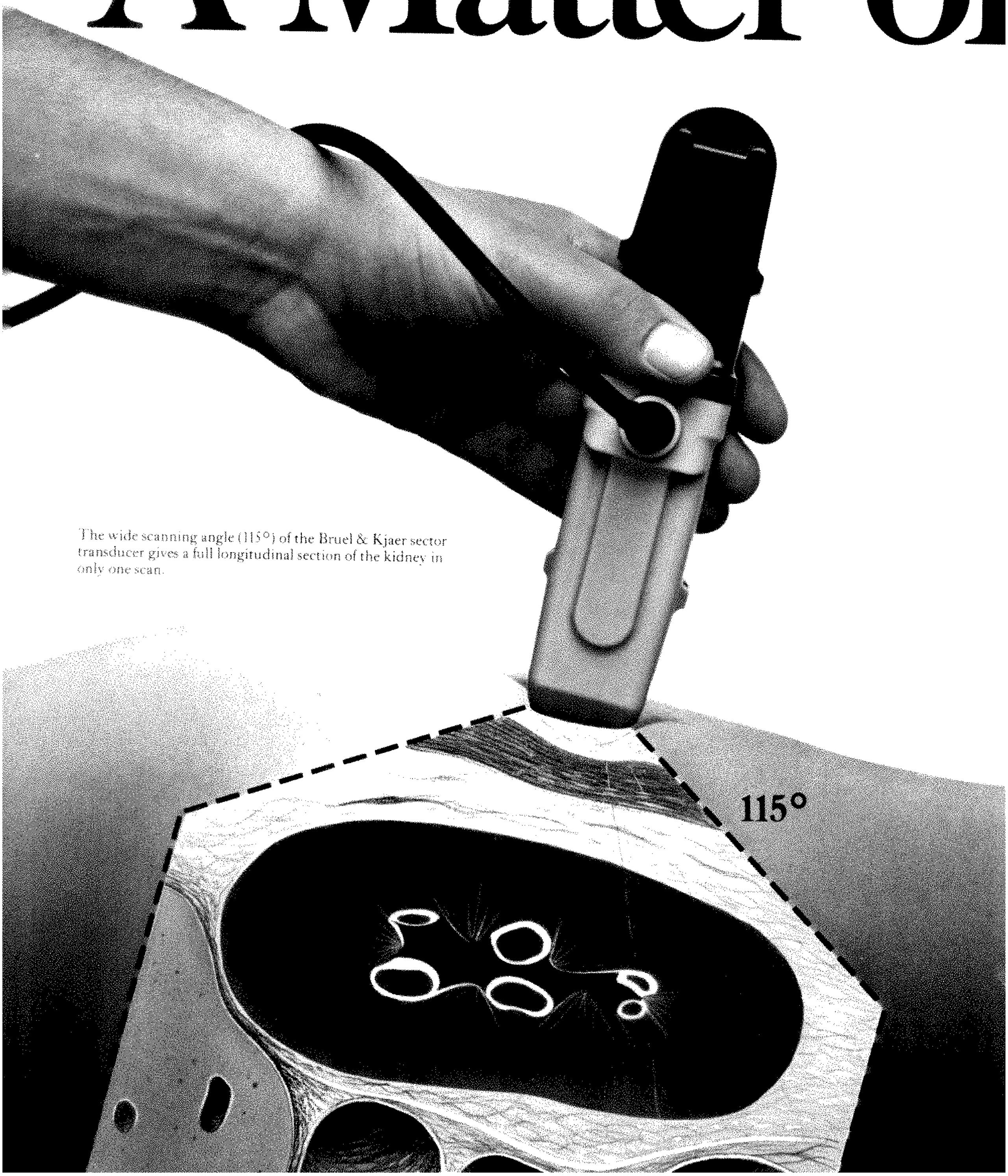

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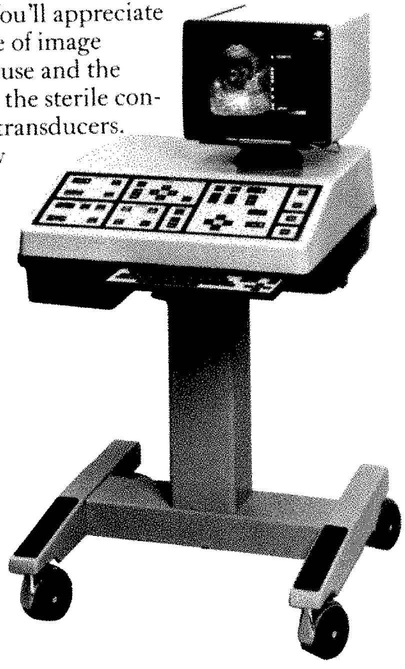

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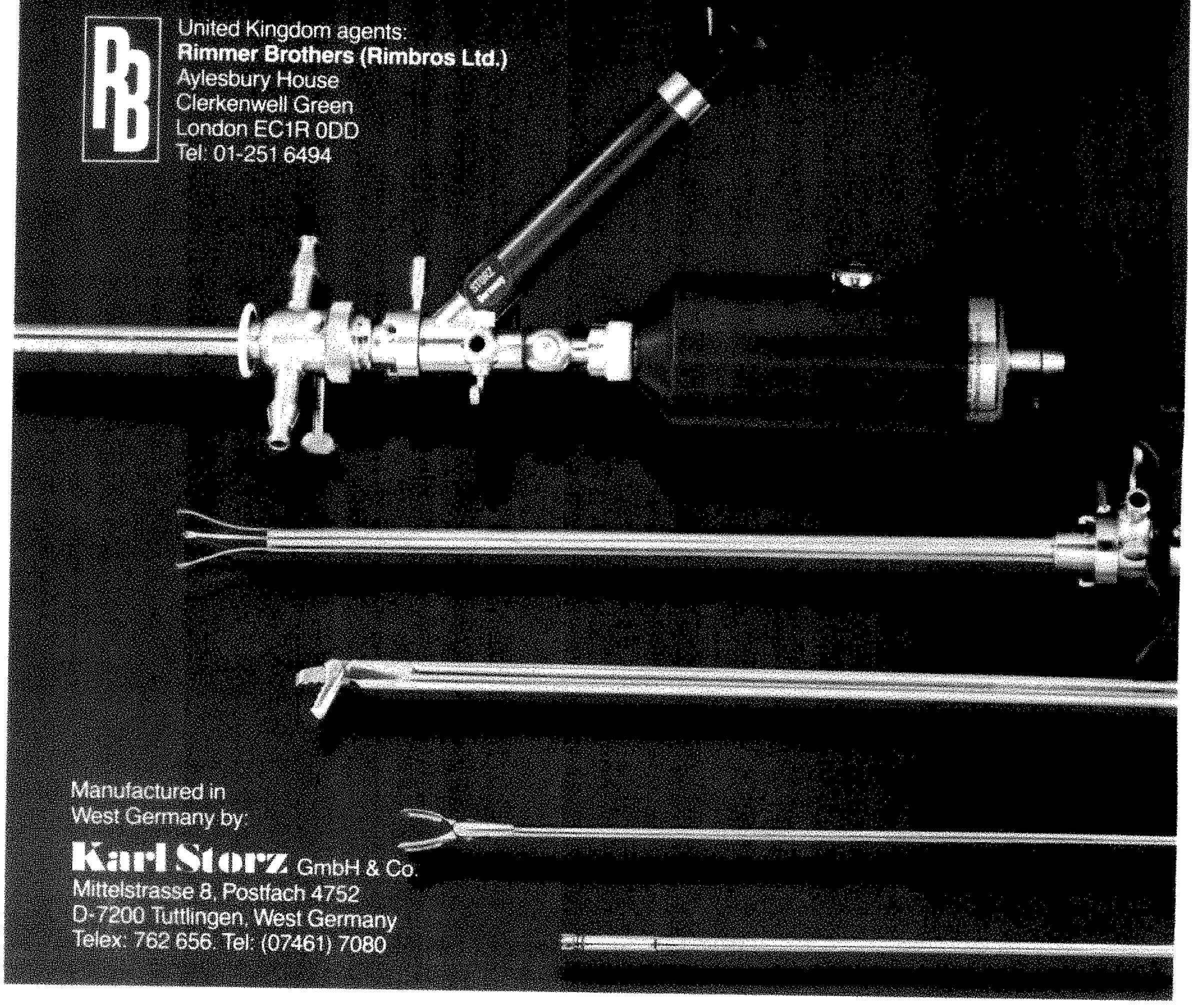

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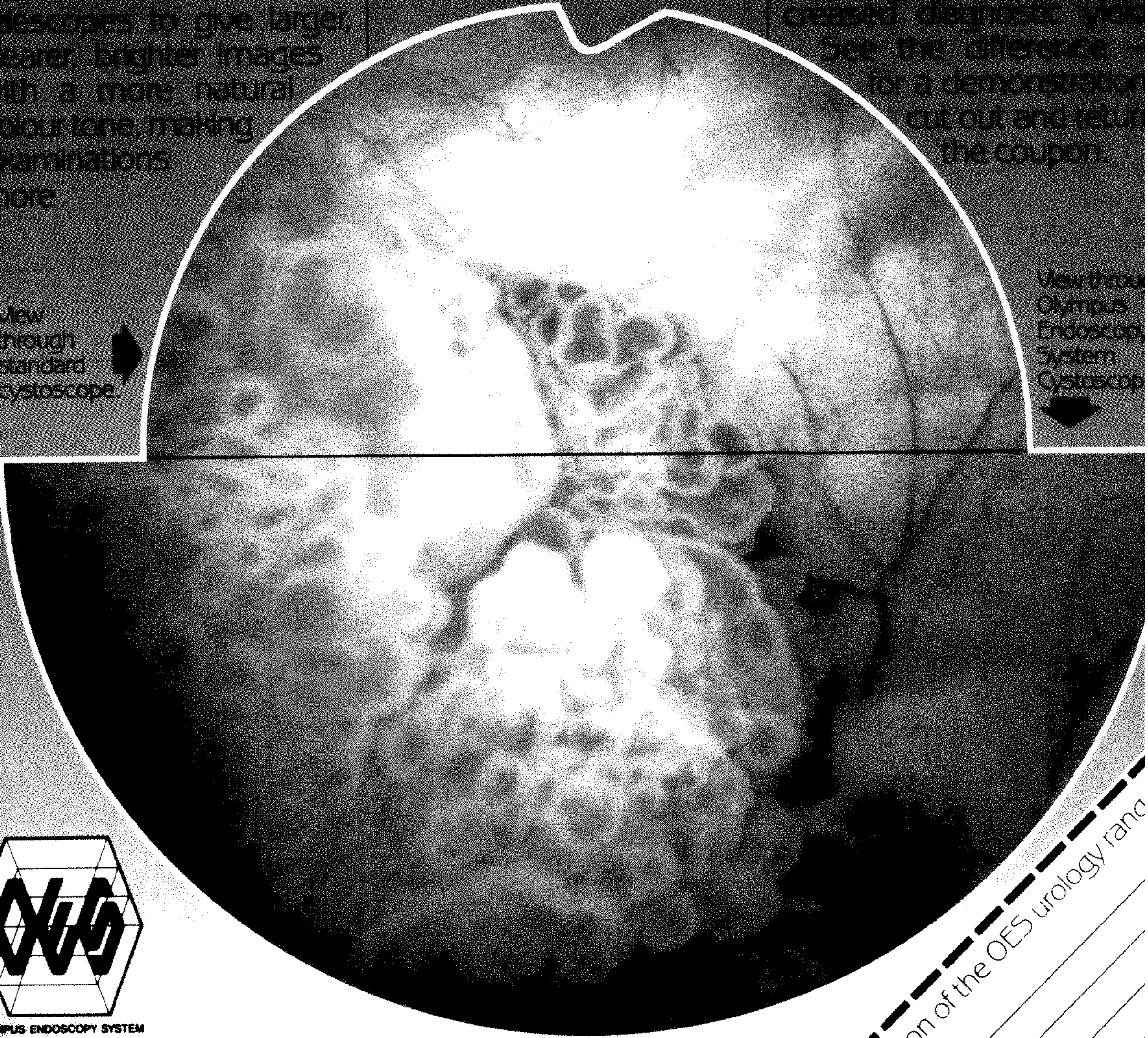

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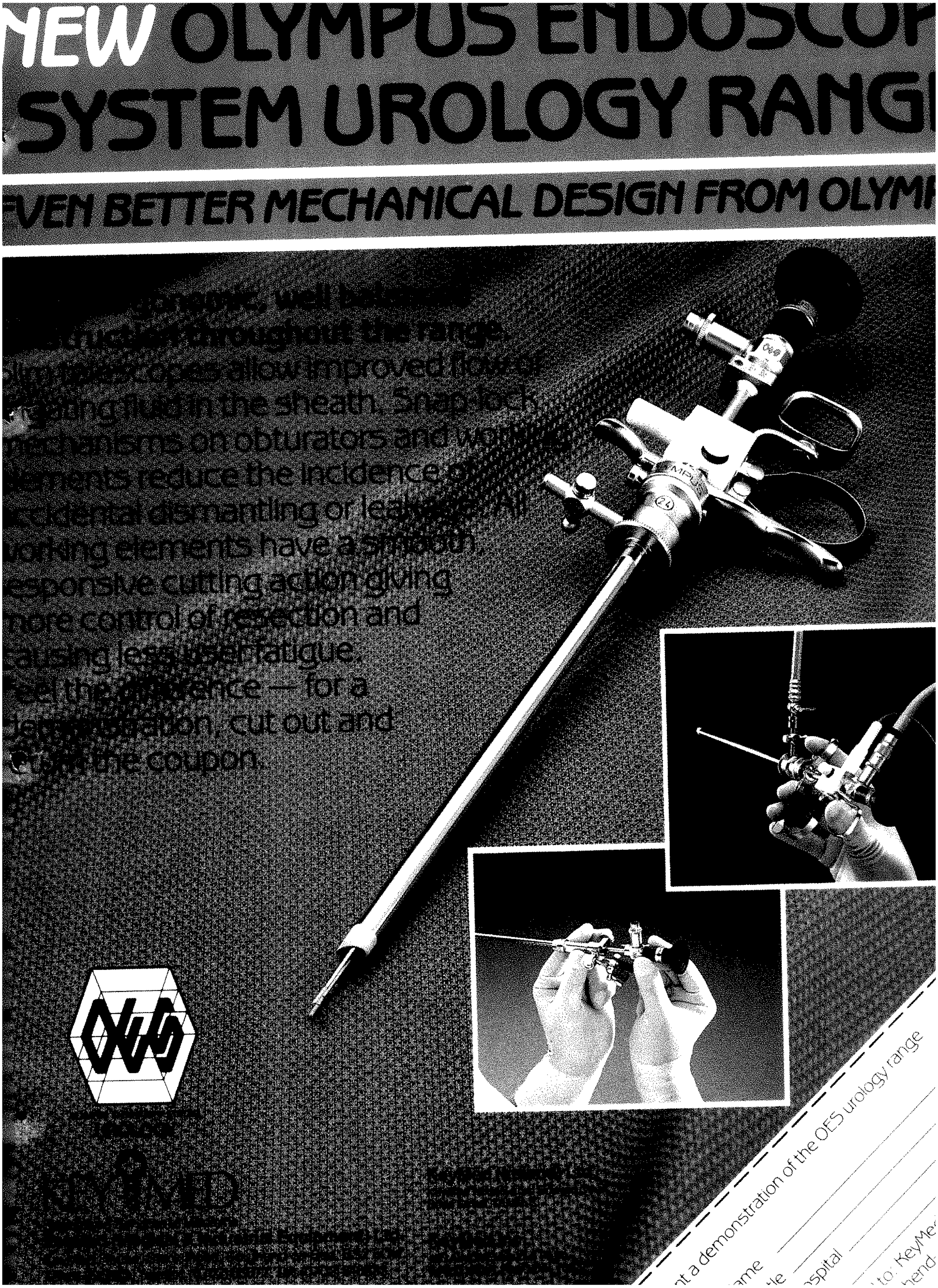

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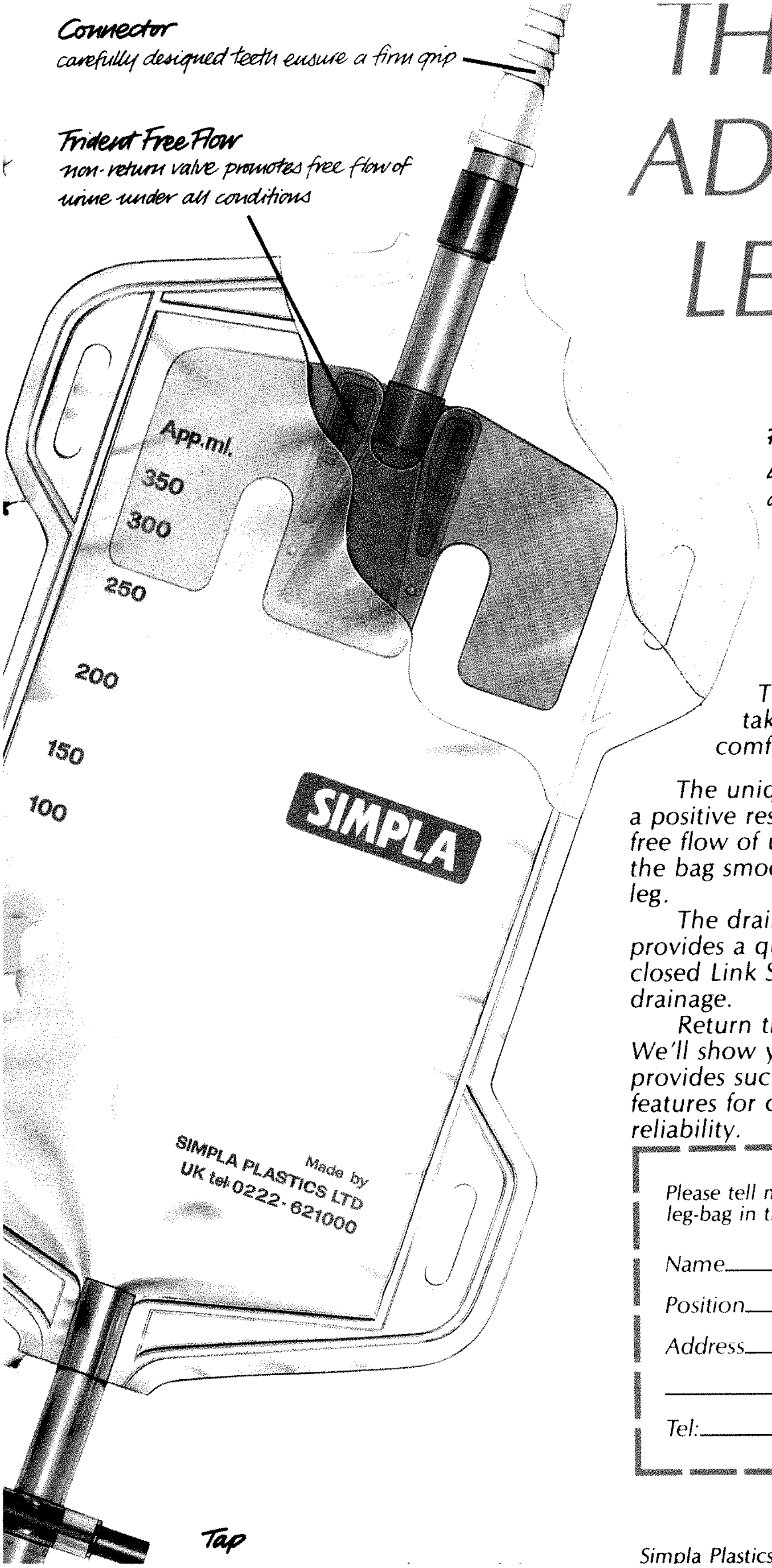

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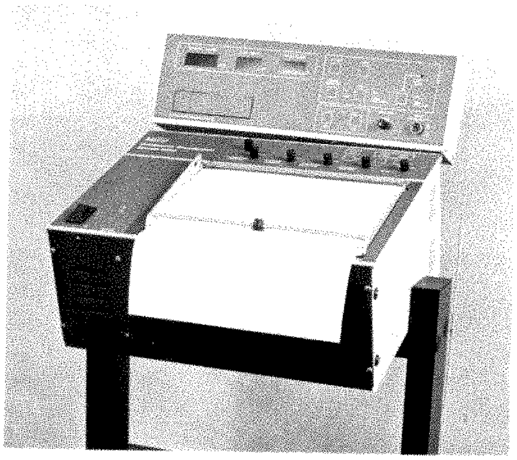

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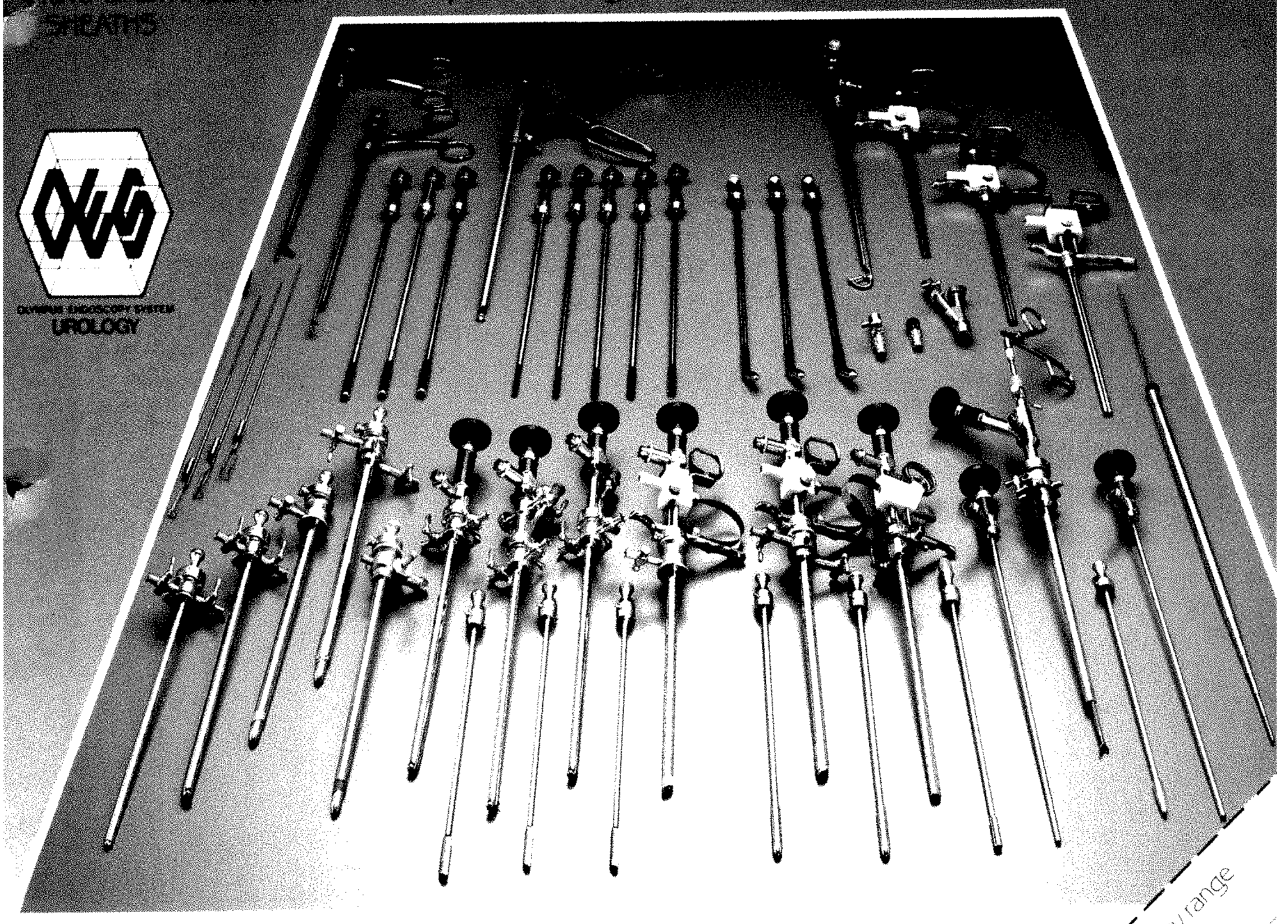

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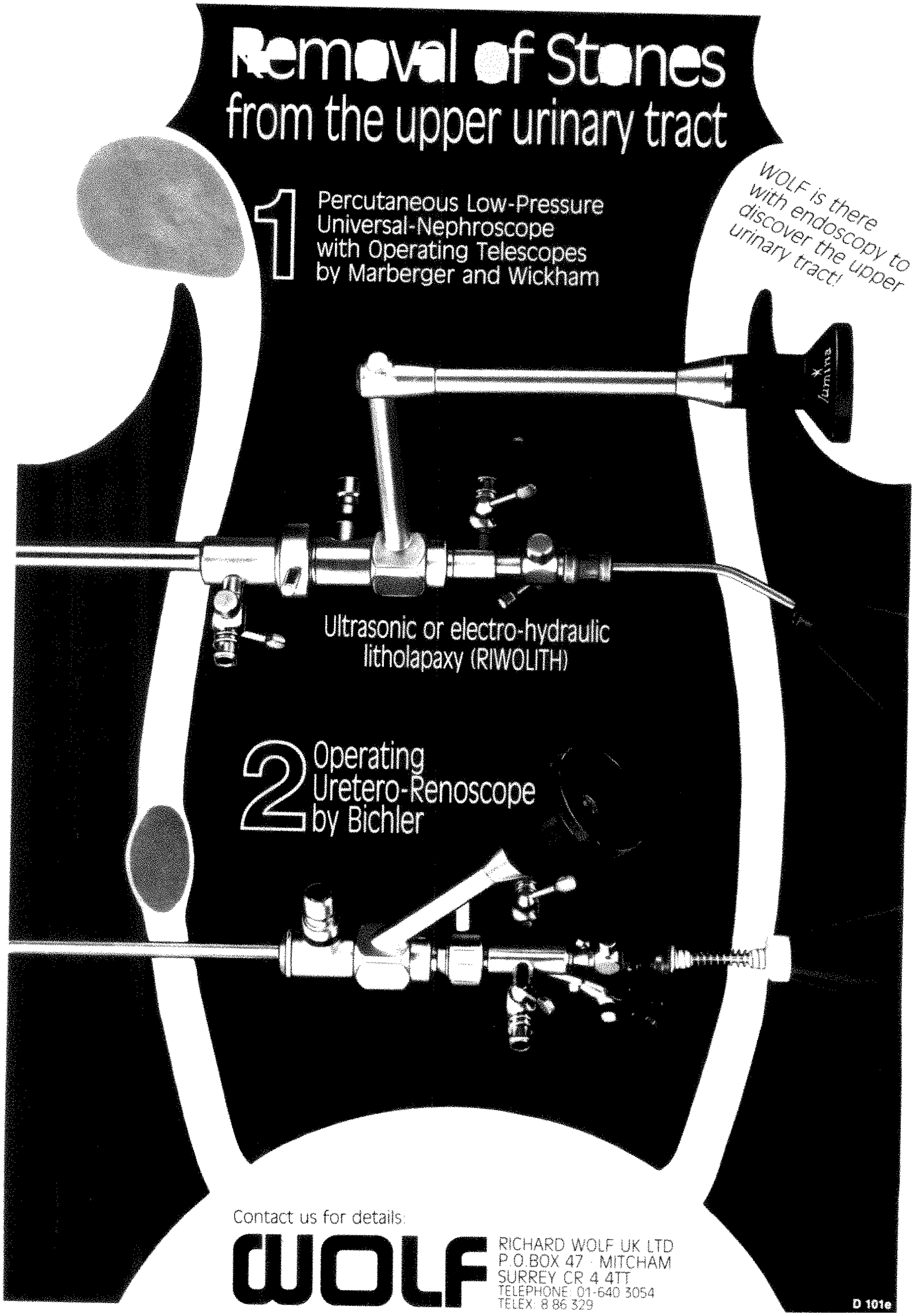

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British Journal of Urology (1985), **57**, 365-369

Familial Pelviureteric Junction Hydronephrosis and its Association with a Duplex Pelvicaliceal System and Vesicoureteric Reflux. A Family Study

J. D. ATWELL

Wessex Regional Centre for Paediatric Surgery, General Hospital, Southampton

Summary—The incidence of pelviureteric junction (PUJ) hydronephrosis and a bifid pelvicaliceal collecting system was determined in the parents and siblings of 19 patients with PUJ hydronephrosis. The high incidence of hydronephrosis in first degree relatives supports the hypothesis that PUJ hydronephrosis is inherited by an autosomal dominant gene of variable penetrance. There is a genetic inter-relationship between PUJ hydronephrosis and a bifid pelvicaliceal system and therefore indirectly between vesico-ureteric reflux and paraureteric diverticula. Ultrasound screening of the children of adults with PUJ hydronephrosis may lead to earlier diagnosis and treatment, thus preventing renal damage.

Genetic factors have an important aetiological role in such renal diseases as polycystic disease and renal calculi of metabolic origin. Family studies in conditions predisposing to urinary tract infection such as a duplex pelvicaliceal collecting system (Whitaker and Danks, 1966; Atwell *et al.* 1974), vesicoureteric reflux (Atwell *et al.*, 1977) and paraureteric diverticula (Atwell and Allen, 1980) have also suggested an inter-relationship between these conditions and that this has a genetic basis.

The present investigation started because of the finding of PUJ hydronephrosis in a father and a son and in a first degree relative of an index patient with a paraureteric diverticulum (Atwell and Allen, 1980). Other first degree relatives were found to have a number of associated congenital anomalies of the urinary tract, *e.g.* vesicoureteric reflux, a bifid collecting system, renal malposition and agenesis, *etc.* If genetic factors are found to be similarly significant, this could explain the fact that PUJ hydronephrosis and vesicoureteric reflux often coexist.

The index patients all presented with symptoms and signs leading to investigations which confirmed the diagnosis of PUJ hydronephrosis. Reflux-induced hydronephrosis was excluded as a primary diagnosis for the index patients.

Patients

Between 1 January 1973 and 31 December 1977, 39 infants and children underwent a pyeloplasty for PUJ hydronephrosis. In 19 families of the patients it was possible to obtain informed consent for a limited IVU to be performed on first degree relatives, *i.e.* parents and siblings of the index patients. In the other 20 families there were difficulties because they had been lost to follow-up or declined to take part in the investigations. Seven of these families had left the country, in one family the index patient had been adopted and in another the index patient died suddenly at home 3 months after his operation (sudden infant death syndrome).

Results

Index patients

There were 12 male and 7 female index patients. In one patient with a left PUJ hydronephrosis there

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were double ureters on the right with vesicoureteric reflux to the lower pole of the kidney which necessitated heminephrectomy. Histological examination of the specimen confirmed the presence of chronic pyelonephritis and renal dysplasia. Another patient had contralateral subtotal reflux. Congenital heart disease was noted in 2 patients: coarctation of the aorta and aortic stenosis. The hydronephrosis was left-sided in 12, right in 5 and bilateral in 2 patients.

First degree relatives

In the 19 families investigated there were 74 first degree relatives (38 parents and 38 siblings). It was possible to perform limited excretion urography in 16 fathers, 17 mothers and 37 siblings. Thus 71 (93%) of the first degree relatives were investigated.

(i) *Association of PUJ hydronephrosis in siblings and parents.* This association was found in 3 fathers and 1 mother. One father had a nephrectomy for his hydronephrosis and one mother had had a pyeloplasty. The other 2 fathers, one of whom is symptomatic, are under medical supervision. Of the 37 siblings investigated 5 were found to have radiological appearances suggestive of incipient hydronephrosis ("saggy bag" renal pelves). None of these has as yet required surgical treatment.

(ii) *Association of duplication of pelvicaliceal system in parents and siblings.* This association was found in 2 of the 19 families. One mother of an index patient had a right bifid ureter and a left bifid renal pelvis and 3 of her 6 children had either a complete or incomplete duplex system. One sibling of an index patient had a bifid renal pelvis.

(iii) *Association of other genitourinary anomalies in siblings and parents.* Infundibular stenosis was found in one father and one sibling. One father had passed a renal calculus and another had significant bilateral dilatation of the lower end of the ureters; a similar finding was noted in one sibling. An orthotopic ureterocele was found in one mother. One mother and 2 siblings had malposition or malrotation of the kidneys and another mother had dilatation of the right upper group of calices, suggesting reflux nephropathy.

In two other families there were significant findings: in the first family an aunt of the index patient had had a non-functioning kidney removed and, in the second, the father of the index patient had ankylosing spondylitis, a disease with a known genetic aetiology and HLA antigen constitution.

The results of these radiological investigations in the relatives showed that 13 had evidence of hydronephrosis, duplication of the pelvicaliceal system or vesicoureteric reflux and its sequelae (Table 1). There was a difference in the incidence of the radiological findings depending upon the sex of the index patient (Table 2). Seven of 24 males (29%) were affected and 2 of 15 females (13%). In the 19 families there were 4 with one parent affected and 15 with neither parent affected. In the former, 2 of 6 siblings had PUJ hydronephrosis and in the latter group 3 of 33 siblings were similarly affected (Table 3).

Table 1 Radiological Findings in First Degree Relatives (Parents and Siblings) of Index Patients with PUJ Hydronephrosis

	Radiological findings		
Relationship to index patients	*Duplication of pelvicaliceal system*	*Vesicoureteric reflux or sequelae*	*PUJ hydronephrosis "baggy pelvis"*
16 fathers	—	—	3 (2)
17 mothers	1	1	1 (1)
38 siblings	2	—	5
71 total relatives	3	1	9 (3)

Table 2 Radiological Findings in Siblings of 13 Males and 6 Female Index Patients with PUJ Hydronephrosis

	Radiological findings	
	Duplication of pelvicaliceal system	*PUJ hydronephrosis*
24 siblings of 13 male index patients	3 (1 (family)	4
15 siblings of 6 female index patients	1	1

Table 3 Radiological Findings in Siblings in Families with One Parent Affected and in Families with Neither Parent Affected

Familial incidence of PUJ hydronephrosis
19 families
4 families: 1 parent affected *2 of 6 siblings affected*
15 families: neither parent affected *3 of 33 siblings affected*

The familial incidence of hydronephrosis is seen in Figure 1. In 2 families the parents with PUJ hydronephrosis were treated by nephrectomy and a pyeloplasty. In 6 other families radiological findings of a large floppy extrarenal pelvis demonstrated a predisposition to hydronephrosis in parents and siblings. The sequelae of vesicoureteric reflux and a duplex collecting system were seen in some families.

Additional families with PUJ hydronephrosis, duplex pelvicaliceal system, vesicoureteric reflux and paraureteric diverticula

The familial association of PUJ hydronephrosis, reflux, a duplex pelvicaliceal system and paraureteric divericula was observed in 9 other families which were not included in the series of patients investigated.,These families also had other genitourinary tract problems such as hypospadias, diverticulum of the posterior urethra and undescended testes. Familial factors are known to be important with hypospadias and undescended testes. The patient with a paraureteric diverticulum whose mother had a pyeloplasty has already been mentioned (Atwell and Allen, 1980).

Discussion

Familial PUJ hydronephrosis is uncommon and only eight examples have been reported (Aaron and Robbins, 1948; Cannon, 1954; Raffle, 1955; Jewell and Buchert, 1962; Simpson and German, 1970; Finn and Carruthers, 1974; Cohen *et al.* 1978). These families were reviewed by Cohen *et al.* (1978) and it was suggested that the method of inheritance of this condition was by an autosomal dominant gene of variable penetrance.

The present investigation into the families of 19 index patients with PUJ hydronephrosis is the first prospective study to be undertaken. It revealed a further seven families with this condition. The data elicited demonstrated that there were 9 first degree relatives in the 7 families with evidence of hydronephrosis (37%). This incidence was higher than expected, although the true incidence in the community is unknown. In a series of 84 families previously investigated with a duplex pelvicaliceal system (Atwell *et al.*, 1974), vesicoureteric reflux (Atwell *et al.*, 1977) or paraureteric diverticula (Atwell and Allen, 1980), there was only one family with a PUJ hydronephrosis in a first degree relative. The findings in this series confirm that PUJ

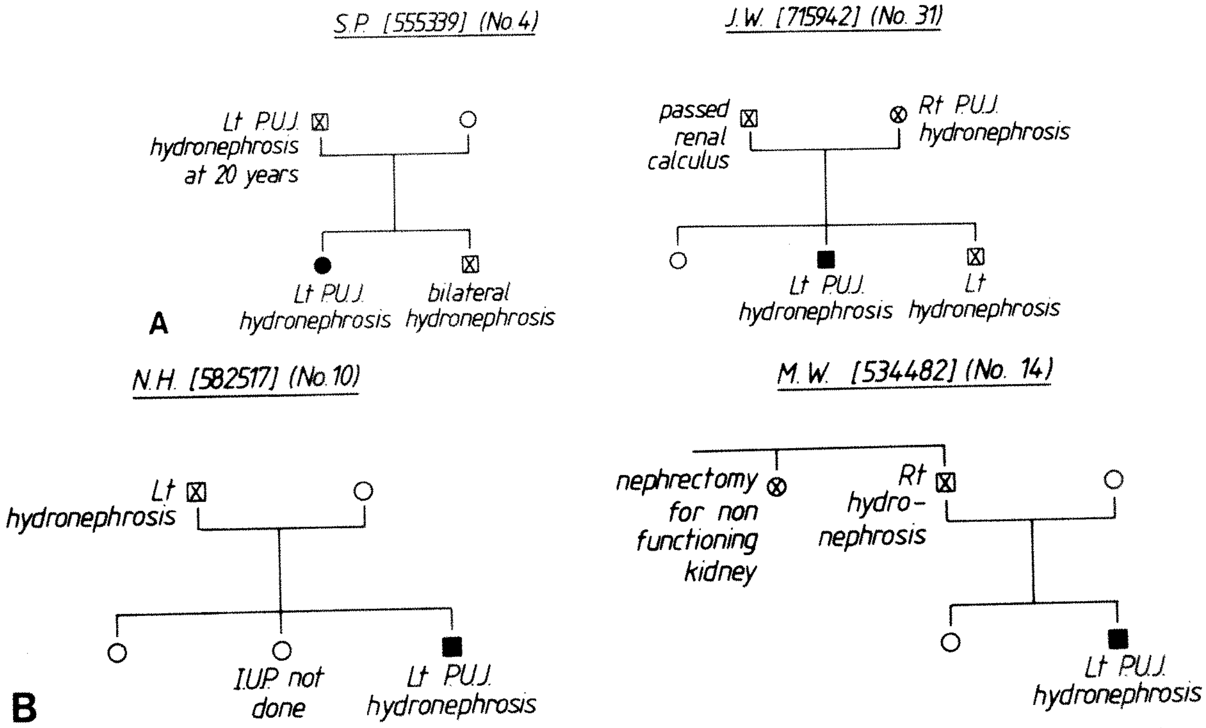

Fig. 1 (A) Family tree of 2 families (Nos 4 and 31) with a father and mother who required surgical treatment for PUJ hydronephrosis. Note the hydronephrosis in siblings in these two families. (B) Two other family trees with hydronephrosis occurring in the fathers of index patients (Nos 10 and 14).

hydronephrosis is a congenital defect with a genetic basis, although as recently as 1958 it was not mentioned in a survey of the genetic origins of renal disease.

Our data support the hypothesis previously reported (Cohen *et al.*, 1978) that the inheritance is by an autosomal dominant gene, since there is a marked difference in the incidence between the families with one parent affected (2 of 6 siblings affected) and those with neither parent affected (3 of 33 siblings affected). The penetrance of the gene is variable, which explains the differences observed in the families.

In the 19 index patients there was no example of PUJ hydronephrosis being associated with a duplex collecting system. The series was small, however, and in a larger personal series of 91 patients 2 were affected and in another series 5 of 117 patients were affected (Thomas *et al.*, 1982). If these two series are combined the incidence is 3.3%, which contrasts with the expected incidence of 0.7%, *i.e.* a 5-fold increase. A duplex collecting system was found in 2 of the families investigated with 5 individuals being affected. This represents a 15-fold increase over the expected incidence and a 10-fold increase amongst the first degree relatives. Thus there appears to be a direct relationship between PUJ hydronephrosis and a duplex collecting system, which suggests that this is of genetic origin. As vesicoureteric reflux and paraureteric diverticula are found in higher numbers in patients with a duplex pelvicaliceal system it seems likely that all of these conditions, including PUJ hydronephrosis, are interrelated. In a personal series of 116 patients with a duplex collecting system we had noted 3 patients with a coexisting PUJ hydronephrosis, thus adding further support to this hypothesis.

The incidence of vesicoureteric reflux in patients with PUJ hydronephrosis varies between 10 and 20%. This clinical association of the two defects is well known but has not often been reported (Lebowitz and Blickman, 1983; Maizels *et al.*, 1984). It is important to differentiate between the two types of hydronephrosis associated with reflux, the first without evidence of obstruction on intravenous urography (reflux-induced hydronephrosis) and the second with obstruction at the pelviureteric junction. In the latter patients the degree of reflux is generally less severe. Delayed drainage can occur with reflux-induced hydronephrosis but is unusual; in the severe examples the renal pelvis becomes grossly distended and the muscle in the wall of the renal pelvis is partially infiltrated with collagenous tissue. When there is a true PUJ hydronephrosis and vesicoureteric reflux, the association could be explained on the theory of a coexisting anomaly on

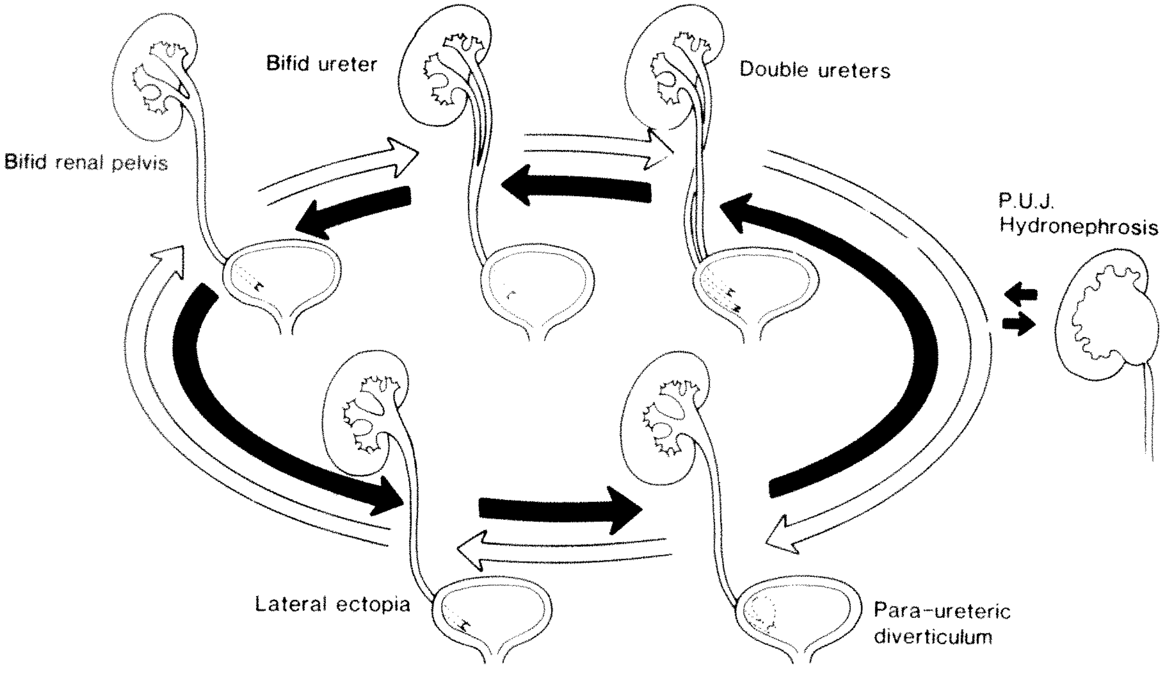

Fig. 2 Genetic inter-relationship between PUJ hydronephrosis and a duplex collecting system, paraureteric diverticular and vesicoureteric reflex.

a common ureteric bud. That this anomaly is of genetic origin is supported by the results of family studies (Whitaker and Danks, 1966; Atwell *et al.*, 1974, 1977; Atwell and Allen, 1980) which have shown an association between a duplex collecting system, vesicoureteric reflux, paraureteric diverticula and now, indirectly, pelviureteric junction hydronephrosis (Fig. 2).

The high incidence of PUJ hydronephrosis in the children of parents with this condition raises the question of the advisability of screening in order to diagnose the condition before significant renal damage has occurred. This is very important, since hydronephrosis may be asymptomatic and many patients have been diagnosed following routine investigations, as occurred in this series. Ultrasonography is a suitable non-invasive investigation for this purpose and it is recommended that the children of adults with PUJ hydronephrosis should be screened in this manner. Whether the relatives of affected children should be screened is more debatable: in our survey 3 of 33 siblings (9%) were affected when neither parent was affected, compared with 2 of 6 siblings (33%) when one parent was affected. Thus the yield of positive results is likely to be less in such a prospective screening programme.

Acknowledgements

I thank the Department of Medical Illustration of the University of Southampton for the figures and the radiologists and radiographers in the Wessex Region who kindly carried out the radiological investigations.

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The Author

J. D. Atwell, FRCS, Consultant Paediatric and Neonatal Surgeon, Wessex Regional Centre for Paediatric Surgery, East Wing, Southampton General Hospital, Shirley, Southampton SO9 4XY.

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Family History of Renal Stones in Recurrent Stone Patients

S. LJUNGHALL, B. G. DANIELSON, B. FELLSTRÖM, K. HOLMGREN, G. JOHANSSON and B. WIKSTRÖM

Departments of Internal Medicine and Urology, University Hospital, Uppsala, Sweden

Summary—A survey was carried out on the family history of renal stones among 380 patients in an out-patient stone clinic, most of whom had experienced frequent recurrences.

In 55.4% of patients at least one first-degree relative had experienced renal stones. A positive family history was more common in females (64.7%) than in males (51.0%) and was particularly apparent in those who had multiple recurrences. It was also significantly more common in female patients with evidence of renal tubular defects (incomplete forms of renal tubular acidosis). Among the ordinary stone patients 18% of the fathers and 8% of the mothers had also formed renal stones. The corresponding figures for female stone patients with renal tubular defects were 40 and 33% respectively. These findings indicate that tubular dysfunction could be an inherited trait that predisposes to the formation of renal stones.

Hypercalciuria or hyperuricosuria was not over-represented among stone formers with a positive family history.

The risk of forming renal stones appears to be increased in individuals with a family history of nephrolithiasis (McGeown, 1960; Resnick *et al.*, 1968; Ljunghall, 1979; Churchill *et al.*, 1980; Marya *et al.*, 1981). This information largely stems from studies of large, unselected populations (Resnick *et al.*, 1968; Ljunghall, 1979; Churchill *et al.*, 1980). Such a design is necessary when the purpose is to establish the true prevalence of the disease, since many of these patients are never admitted to hospital (Ljunghall, 1977). However, in population-based surveys the patients generally have mild to moderate stone disease and for obvious reasons it is not possible to perform detailed clinical or laboratory examinations. The formation of a stone is generally considered to be a multifactorial event but the nature, in biochemical terms, of the possible inherited predisposition is not known.

Against this background we have extended our previous studies of the unselected male population (Ljunghall, 1979) to patients with more severe disease admitted to a stone clinic.

Patients and Methods

The study comprised 380 consecutive patients who attended our out-patient stone clinic. There were 253 males and 127 females; 26.3% had a history of multiple (more than 10) stone recurrences. The age and sex distribution are shown in Figure 1. All patients were investigated according to our general protocol, which included measurement of serum and urinary electrolytes and uric acid, a quantitative test for cystinuria, urine culture and X-ray of the urinary tracts. Hypercalciuria, defined as a 24-h urinary calcium $\geqslant 7.5$ mmol, was found in 130 patients (34.2%), whereas hyperuricosuria (urinary urate $\geqslant 4.5$ mmol/24 h) appeared in 86 patients (23.7%). Urinary tract infection of clinical importance was considered to have been present in 98 patients (28%). A short-term ammonium chloride test (Backman *et al.*, 1980) was performed on 223

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Table 1 Frequency (%) of Abnormal Laboratory Findings in Stone Patients Separated with Regard to Sex and Number of Stones

	Males		*Females*		*All*	
	All	*≥ 10 stones*	*All*	*≥ 10 stones*	*All*	*≥ 10 stones*
Number of patients	253	71	127	29	380	100
Hypercalcuria	39.5*	38.0*	18.9	13.8	34.2	31.0
Hyperuricosuria	28.5†	21.1	14.2	13.7	23.8	19.0
Defective renal acidification	19.4*	29.6*	49.6	69.0	30.0	40.0**
Urinary tract infection	14.3*	15.7‡	43.3	37.9	28.0	22.0

* $P < 0.001$. † $P < 0.01$. ‡ $P < 0.05$ *vs* females. ** $P < 0.05$ *vs* patients with < 10 stones.

Table 2 Family History (%) of Renal Stones among Stone Formers Separated with Regard to Sex, Multiple (≥ 10) Stones and Laboratory Findings

Laboratory findings	*Males*		*Females*	
	All	*≥ 10 stones*	*All*	*≥ 10 stones*
Urine calcium				
≥ 7.5 mmol/24 h	50.7	59.2	66.0	ND (4/4)
< 7.5 mmol/24 h	51.2	59.1	63.1	80.0
Urine urate				
≥ 4.5 mmol/24 h	50.0	53.3	75.0	ND (3/4)
< 4.5 mmol/24 h	51.4	60.7	62.7	84
Renal acidification				
defective	56.0	50.0	83.3†, **	84.6*
normal	53.7	64.7	48.5	ND (4/6)
not studied	46.1	56.5	60.6	ND (9/10)
Urinary tract infection	29	36.3	57‡	63.6
All patients	51.0	59.2	64.7*	82.8*

* $P < 0.05$. † $P < 0.01$. ‡ $P < 0.001$ compared with males.
** $P < 0.001$ compared with female stone formers with normal renal acidification.
ND = Not determined because the group constituted less than 10 patients.

patients, primarily on those with early onset of stones and/or frequent recurrences. No patient had complete renal tubular acidosis (RTA) but the urinary acidification capacity was impaired in 67 patients (30%). The test discloses the incomplete forms of both proximal and distal RTA. Since these types were equally common and no particular features separated them in this study, they have been considered together.

Hypercalciuria was more common in males and defective renal acidification in the females. Patients with multiple recurrences (of both sexes) more often had incomplete RTA than had those with fewer stones (Table 1).

Patients were asked during a routine visit to the clinic about the occurrence of stones in their first-degree relatives. Since previous studies (Ljunghall, 1979) showed that this type of information was usually accurate, *i.e.* there was no over-reporting of stones, the patients' history was not further verified, nor were any attempts made to obtain direct information from the 2412 first-degree relatives of the 380 patients in this study.

A positive family history was considered to be present when at least one of the first-degree relatives had experienced a renal stone. On the other hand, a negative history was accepted only if the patients did possess information about their first-degree relatives. Twenty-five female and 57 male patients (21.5%) either had no siblings or did not have information about the possible occurrence of stones in their other first-degree relatives.

The chi-square test was used for comparison of proportions.

Results

Of the 380 stone patients 55.4% reported that at least one of their first-degree relatives had a history of renal stones.

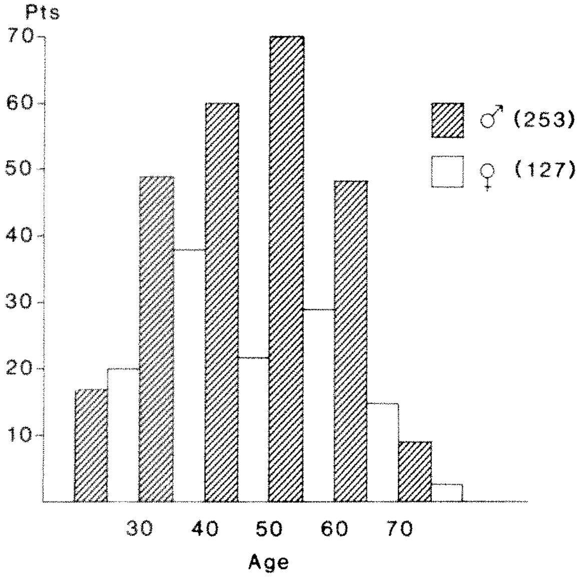

Fig. 1 Age and sex distribution.

A positive family history was more common in female stone patients (64.7%) than in males (51.0%) and was more common in those with frequent recurrences (Fig. 2).

The family history of stones in the males appeared to be unrelated to laboratory findings, *i.e.* there was no over-representation in those with hypercalciuria, hyperuricosuria and impairment of renal acidification (Table 2). In the female stone patients, however, a positive family history was significantly more common in those with the incomplete forms of renal tubular acidosis (Table 2).

When the prevalence of stones was calculated in the relatives, no differences were found among the relatives of male stone patients when divided according to laboratory findings, *i.e.* approximately 17% of their fathers, 8% of their mothers, 15% of their brothers, 6% of their sisters and 2% of their children had also experienced renal stones regardless of the underlying biochemical abnormality in the probands (Fig. 3). In the relatives of female stone patients a different picture emerged. A markedly higher figure was reported from those females with impaired renal acidification, where more than 40% of the fathers and 33% of the mothers had also formed renal stones (Fig. 3).

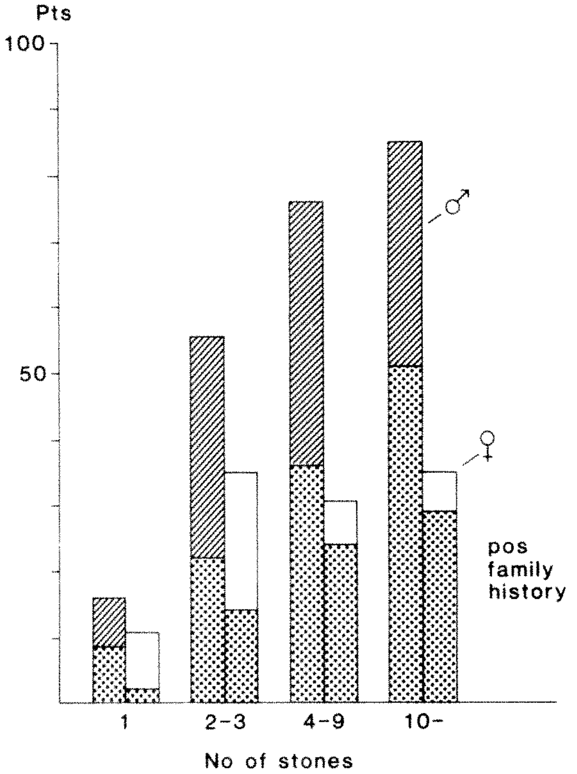

Fig. 2 Patients divided according to sex, number of stones and positive family history of stones (lower part of bars).

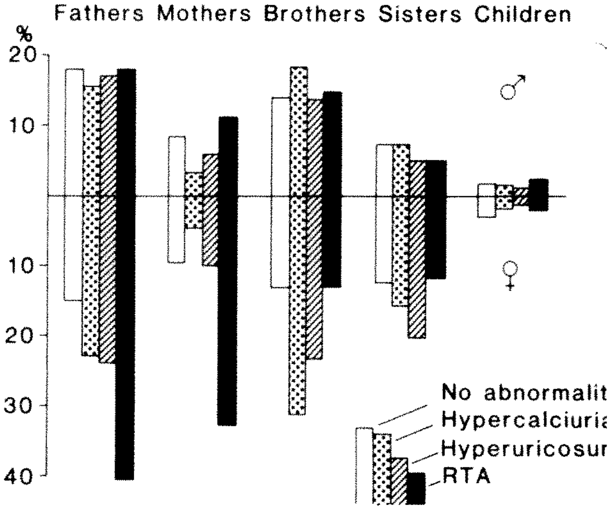

Fig. 3 Occurrence of renal stones in first-degree relatives of stone patients divided according to underlying biochemical abnormalities.

Discussion

A family history of stones was obtained in more than half of the patients. It was more common in females than in males, particularly in those with many stones.

Churchill *et al.* (1980) reported similar sex differences in an epidemiological survey. They found that in an unselected population of stone formers a positive family history was reported by 39% of all patients. The prevalence of renal stones in the parents of male stone formers was not higher than expected from studies of the stone-free population. The female stone formers, however, had an affected parent significantly more often than their stone-free counterparts.

The fact that renal stone formation runs in certain families does not necessarily imply that it is inherited. Members of the family share not only genetic information but also tend to adopt similar ways of living, *e.g.* as regards dietary habits. We have previously reported that the spouses of such families also appear to have an increased risk of stones (Ljunghall, 1979). Hence we prefer the term family history to inheritance.

Among female stone formers, in the present study, a family history of stones was obtained from almost two-thirds and was even more common in those who had evidence of renal tubular dysfunction. Complete distal renal tubular acidosis can be inherited and is known to cause renal stones or nephrocalcinosis (Feest and Wrong, 1975). We have previously reported that renal tubular defects (either tubular proteinuria or incomplete defects in urinary acidification) are common among recurrent renal stone formers (Backman *et al.*, 1980). The incomplete forms of RTA can only be detected by an ammonium chloride load (Backman *et al.*, 1976). Among our stone patients those with incomplete RTA tended to have more severe stone disease than the idiopathic stone formers and there was also an over-representation of young females in this group (Backman *et al.*, 1980).

Our finding that these patients also have a strong family history of renal stones indicates that tubular dysfunction can be inherited and that it is of pathogenetic importance in the development of renal stones. Systematic studies of renal tubular function in the stone-forming and stone-free relatives of these patients should be performed to corroborate this hypothesis.

Apart from this observation there was no apparent correlation between the laboratory profile and the family history of renal stones. In particular, neither hypercalciuria nor hyperuricosuria occurred significantly more often in those with stones in their first-degree relatives. This confirms findings from previous epidemiological studies (Ljunghall, 1979). Nevertheless, there have been reports of familial hypercalciuria (Weinberger *et al.*, 1981). Coe *et al.* (1979) found increased urinary calcium in half of all investigated relatives of stone formers with idiopathic hypercalciuria. However, there was no association between hypercalciuria and stone formation in the relatives, although a stone-forming tendency was much more common in the first-degree relatives of stone formers than in other relatives. In addition, the study by McGeown (1960) revealed no tendency for hypercalciuria to be more common in those with a positive family history of renal stones. Investigation of renal tubular function was not performed in these studies and familial factors other than the presence of hypercalciuria could have been important.

There has been a marked increase in the incidence of renal stones during the last few decades (Ljunghall, 1978), presumably related to the increased standard of living, but the precise nature of this association has not been established. "Pure" genetic causes of stone formation are presumably rare within the large number of unselected stone formers. The tendency towards over-representation of renal stones in certain families might therefore be thought to reflect an inherited predisposition to stone formation which becomes manifest only when other (environmental?) factors are also present. It is thus not remarkable that the majority of "idiopathic" stone formers with a family history of renal stones cannot be distinguished by laboratory tests. The higher prevalence of a positive family history in female stone formers is consistent with a multifactorial model for stone formation, where affected individuals of the sex which is less often affected will tend to be more extreme deviants in terms of genetic liability and the genetic risk to their relatives will be correspondingly higher.

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The Authors

S. Ljunghall, MD, Associate Professor and Consultant, Section of Endocrinology.

B. G. Danielson, MD, Associate Professor and Consultant, Section of Nephrology.

B. Fellström, MD, Assistant Professor and Registrar, Section of Nephrology.

K. Holmgren, MD, Registrar, Department of Urology.

G. Johansson, MD, Assistant Professor and Registrar, Section of Nephrology.

B. Wikström, MD, Assistant Professor and Registrar, Section of Nephrology.

Requests for reprints to: S. Ljunghall, Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden.

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Allopurinol Treatment of Renal Calcium Stone Disease

B. FELLSTRÖM, U. BACKMAN, B. G. DANIELSON, K. HOLMGREN, G. JOHANSSON, M. LINDSJÖ, S. LJUNGHALL and B. WIKSTRÖM

Departments of Internal Medicine and Urology, University Hospital, Uppsala, Sweden

Summary—Thirty-one calcium stone patients were treated with 300 mg allopurinol daily during a mean follow-up period of 2 years. They were also given advice on diet and fluid intake. The effects on the recurrence rate of stones were compared with the effects on the recurrence rate in 43 calcium stone patients who were given similar advice on diet and fluid intake but were not treated with allopurinol. In both groups there was a reduction in the recurrence rate but no difference between patients treated with allopurinol and the control group. Some patients with only hyperuricosuria prior to treatment seemed to benefit from allopurinol treatment, whereas those with hypercalciuria continued to form stones with the same frequency. Allopurinol treatment in calcium stone disease appears less effective than treatment with thiazides, magnesium hydroxide or orthophosphate.

Many treatments have been used to prevent stone formation in the urinary tract. Treatment with orthophosphate (Smith *et al.*, 1980; Wikström *et al.*, 1984), thiazides (Ljunghall *et al.*, 1981) and magnesium hydroxide (Johansson *et al.*, 1980) has been shown to be effective in preventing the recurrence of calcium stone disease. Allopurinol has been reported to be effective in the treatment of uric acid stones in the renal tract (de Vries *et al.*, 1966), whereas variable results have been achieved in the treatment of calcium-containing urolithiasis. The purpose of the present study was to treat calcium stone formers with allopurinol, irrespective of whether they were hyperuricosuric or hypercalciuric when entering the study.

Patients and Methods

Thirty-two consecutive calcium stone patients were recruited for allopurinol treatment. There were 23 males aged 44 ± 20 years and 8 females aged 45 ± 19 years. Six patients had both hyperuricosuria and hypercalciuria, eight had only hyperuricosuria, five only hypercalciuria and 12 had neither of these conditions. They were all recurrent stone formers, i.e. they had passed at least two stones before being considered for prophylactic treatment in the form of 300 mg allopurinol (Zyloric) daily. The patients were recommended to avoid an excessive intake of calcium-rich foods and to try to increase their fluid ingestion. Follow-up was performed at our outpatient stone clinic at intervals of 6 months. The average time on treatment was 2 years (range 1.0-3.5 years). Thirty-three patients were included in the treatment group but two were subsequently excluded because of side effects consisting of a rash.

No placebo treatment was given. Results in the allopurinol group were compared with those in 43 recurrent stone patients who had been given similar advice regarding diet and fluid intake. These patients had a similar frequency of hypercalciuria, whereas hyperuricosuria was less common (10%) than in the allopurinol-treated patients. Follow-up of these control patients was identical to that of the patients on allopurinol treatment. Informed consent was obtained in all cases.

Before commencing treatment and during the follow-up period, measurements were made of serum and urinary electrolytes, but urinary oxalate was not measured. An annual radiographic investigation of the urinary tract was performed during follow-up. A stone episode was defined as the spontaneous passage, surgical removal or radiographic

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visualisation of a stone. Stone episodes prior to treatment were traced from case histories and previous radiographs. Stone operations included nephro-, pyelo- and uretero-lithotomy together with endoscopic stone removal. Hyperuricosuria was defined as a urinary excretion exceeding 4.5 mmol/24 h in males and 4.0 mmol/24 h in females (Fellström *et al.*, 1982b). Hypercalciuria was defined as a urinary calcium exceeding 7.5 mmol/24 h in males and 7.0 mmol/24 h in females. Student's t test was used to compare mean values and a chi-square test to compare frequencies.

Results

In patients treated with allopurinol the recurrence rate decreased from 60 stones/100 patient years before treatment to 47 stones/100 patient years on treatment. Altogether 16/31 patients (51%) had no recurrences during follow-up (Table 1). Subdividing the patients with respect to the excretion of urate and calcium prior to treatment yielded small subgroups with no statistically significant differences in recurrence rate during treatment. Five of six patients with both hyperuricosuria and hypercalciuria experienced recurrences during follow-up (Table 1). On the other hand, 6/8 patients with hyperuricosuria but without hypercalciuria were recurrence-free during follow-up.

Table 1 Effects of 2 Years' Allopurinol Treatment on Stone Recurrence in Calcium Stone Patients, Subdivided with Respect to Uricosuria and Calciuria, and Compared with Control Patients Given no Medical Treatment

	Number of patients	*Patients with stone recurrences (number)*	*(%)*
Allopurinol patients	31	15	49
HU + HC	6	5	83
HU + NC	8	2	25
HC + NU	5	2	40
NU + NC	12	6	50
HU	14	7	50
NU	17	8	47
HC	11	7	64
NC	20	8	40
Control patients	43	17	40

HU = hyperuricosuria; NU = normouricosuria; HC = hypercalciuria; NC = normocalciuria.

The 43 control patients had a stone episode rate of 60 stones/100 patient years before admission to the stone clinic and this was reduced to 25 stones/100 patient years during follow-up. After a 2-year period 26/43 patients (60%) reported no recurrences. There was no statistical difference between patients treated with allopurinol and control patients.

Patient compliance was considered to be good. In all patients treated with allopurinol a decrease in urinary urate became apparent after the first 6 months of treatment. The mean decrease was 1.2 mmol/24 h ($P<0.001$). There was no effect on the urinary excretion of calcium (Table 2).

Table 2 Urinary Excretion of Urate and Calcium (mmol/24 h) during Treatment with Allopurinol 300 mg Daily in 31 Calcium Stone Formers (mean ± SD)

	Before treatment	*On treatment*
Urate	4.0 ± 1.2	2.8 ± 0.8*
Calcium	6.0 ± 2.6	5.8 ± 2.8

* $P<0.001$.

Discussion

Allopurinol is a competitive inhibitor of xanthine oxidase, which catalyses the conversion of hypoxanthine to xanthine and xanthine to uric acid (Kelley, 1975). The usual effect in man is a decrease in uric acid production, which can be monitored by a decreased level of serum urate and urinary urate. Treatment with allopurinol is well documented in patients with uric acid stones (de Vries *et al.*, 1966) and uric acid nephropathy.

Several mechanisms by which allopurinol could be effective in calcium stone formation have been suggested (Table 3). Many of these are based on the assumption that a solid or a colloidal phase of uric acid or sodium acid urate would appear in the urine of calcium stone formers. These mechanisms include an adverse effect on inhibition by urate through a binding of inhibitors of calcium oxalate crystal growth and aggregation, whereby a reduction in macromolecular inhibitors in the urine would occur (Robertson *et al.*, 1976; Pak *et al.*, 1979; Fellström *et al.*, 1982a). The other major theory concerns the epitaxial growth of calcium oxalate on urate microcrystals, based on structural similarities of the crystals (Lonsdale, 1968) and *in vitro* experimental studies (Pak and Arnold, 1975). Furthermore, it has been suggested that a reduction in the urinary excretion of oxalate may occur, possibly due to a metabolic pathway of purines to

Table 3 Possible Mechanisms for Allopurinol in Calcium Stone Disease

1. *Adverse effect on inhibition by urate*
   Inhibition of aggregation
   Formation product ratio increase
   Crystal growth inhibition
   Binding of inhibitors
2. *Epitaxis calcium oxalate—urate*
   Stone analysis
   Crystal structure
   In vitro experiment
   In vivo experiment
3. *Oxalate reduction*
4. *Pyrophosphate increase*
5. *No direct effect*

oxalate (Scott *et al.*, 1978; Tomlinson *et al.*, 1981), but this has not been confirmed. There have also been case studies where urinary pyrophosphate has been shown to increase on allopurinol treatment (Pak, 1981), but allopurinol *per se* does not seem to exert any inhibitory effect on calcium oxalate crystal growth (Finlayson *et al.*, 1979).

Most of the theories connecting urate metabolism to calcium stone disease are based on the assumption that a solid or a colloidal phase of sodium acid urate does exist in urine. This has not been finally proved and urate crystals are not often found in the urine of calcium stone formers. Even if it were true, one would expect urate to be a risk factor for calcium stone disease. In order to be considered a risk factor, urinary urate should be higher in stone formers than in healthy controls, and the risk of forming stones should increase with increasing urate levels. A comparison of the frequency of hyperuricosuria in various reports suffers from a lack of unity in defining hyperuricosuria. In the literature the upper limit of urinary urate has varied between 3.6 and 4.75 mmol/24 h. Conflicting results have therefore also been reported on whether the urinary urate in stone formers differs from that in healthy controls (Fig.). We found no difference in the urinary excretion of urate between stone formers and controls, subdivided with respect to sex (Fellström *et al.*, 1982b), which may be one reason why treatment with allopurinol seems to be of limited value in our patients.

In the present study, which was not randomised, a comparison was made with control patients given only the same dietary and fluid advice as the patients treated with allopurinol, and there was no difference in the effect on stone recurrence rates. In both groups the recurrence rates were reduced, but there was no difference between the groups. It should be pointed out that during a short follow-up there is always an apparent reduction in recurrence rate, regardless of whether treatment is effective or

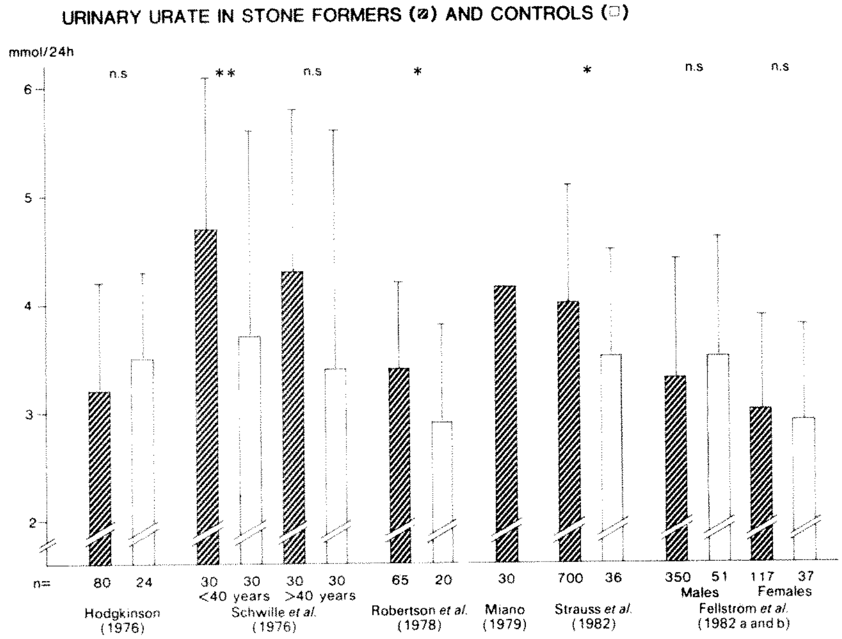

Fig. Urinary urate in calcium stone formers and healthy controls by various investigators (mean +SD). Stone formers (▨), Controls (☐)

not. Patients with significant hypercalciuria, particularly in combination with hyperuricosuria, seemed to do particularly badly on only allopurinol treatment. Furthermore, six patients (6/8) with pure hyperuricosuria seemed to benefit from allopurinol treatment. However, there were only eight patients with pure hyperuricosuria, and this group of patients would have to be expanded before any firm conclusion could be drawn.

In a randomised study in calcium stone patients with hyperuricaemia (Smith, 1977) it was originally concluded that a beneficial effect was achieved with allopurinol. However, in a recent update the author concluded that only a small number of patients with hyperuricosuria did benefit from allopurinol treatment (Smith, 1983). In the studies by Coe (1977) and Pak *et al.* (1981), patients with hyperuricosuria were treated with allopurinol alone, but patients with concomitant hyperuricosuria and hypercalciuria were given a combination of allopurinol and thiazides. This was reported to be effective when compared with the results in control patients who were given only dietary and fluid advice. Two randomised studies with allopurinol have recently been presented. In one of these, comprising 15 patients treated with allopurinol or placebo for 3 years, no beneficial effects from allopurinol were noted (Miano *et al.*, 1984). However, in the other controlled study (Ettinger *et al.*, 1984), 72 calcium stone patients were assigned to allopurinol or placebo treatment and a substantial decrease in the stone recurrence rate was found in the placebo group, together with an even more pronounced reduction in the allopurinol group.

In summary, contradictory results have been achieved in the treatment of calcium stone disease with allopurinol. From the present study it is concluded that allopurinol is not effective in the treatment of calcium stone disease as a whole, and seems far less effective than treatment with thiazides, orthophosphate or magnesium hydroxide.

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The Authors

B. Fellström, MD, Assistant Professor, Registrar in Nephrology.

U. Backman, MD, Associate Professor, Consultant in Nephrology.

B. G. Danielson, MD, Associate Professor, Consultant in Nephrology.

K. Holmgren, MD, Registrar in Urology.

G. Johansson, MD, Assistant Professor, Registrar in Nephrology.

M. Lindsjö, MD, Resident in Nephrology.

S. Ljunghall, MD, Associate Professor, Consultant in Internal Medicine.

B. Wikström, MD, Assistant Professor, Registrar in Nephrology.

Requests for reprints to: B. Fellström, Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden.

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Function of Human Autologous Kidney Grafts after Extracorporeal Preservation with Sacks' II Solution

T. RANCH, H. BRYNGER, G. GRANERUS, Ch. HENRIKSSON, A. E. NILSON and S. PETTERSSON

Departments of Urology, Surgery I, Clinical Physiology and Uroradiology, Sahlgrenska Sjukhuset, University of Göteborg, Göteborg, Sweden

Summary—The function of 18 human kidney grafts was studied before and 3 months after autotransplantation without prior bench surgery on the parenchyma or the vessels. Kidney protection was accomplished by pre-treating the patient with mannitol and low molecular weight dextran solution and flushing the kidney with a Xylocaine-heparin mixture and cold Sacks' II solution. The mean cold ischaemia time was 239 min (range 140-345 min).

The glomerular filtration rate (GFR) remained unchanged post-operatively in terms of both total and split kidney GFR. Proximal and distal tubular integrity, as studied by determination of beta$_2$-microglobulin excretion and concentration ability respectively, was also preserved.

Renal autotransplantation is based on the experience of renal allografting from which both preservation procedures and surgical techniques have been learned. Since the autotransplanted human kidney has often been subjected to extensive extracorporeal surgery, including resection of parenchyma and tumours (Calne, 1973; Brynger *et al.*, 1981; Novick *et al.*, 1981), multiple nephrotomies (Turini *et al.*, 1977; Pettersson *et al.*, 1981) and vascular reconstruction (Belzer *et al.*, 1974; Blohmé *et al.*, 1981; Novick *et al.*, 1981) before revascularisation, it has so far not been possible to perform a systematic evaluation of the preservation procedure.

The introduction of direct pyelocystostomy in renal autotransplantation has meant that new categories of renal disorder are now treated by autotransplantation without preceding bench surgery on the parenchyma or the vessels (Pettersson *et al.*, 1983a and b, 1984). These kidneys are therefore suitable for an evaluation of the efficiency of extracorporeal preservation of human renal grafts.

Patients and Methods

Since 1977, 20 kidneys in 20 patients have been autotransplanted with a direct anastomosis between the renal pelvis and the bladder. There were 3 females and 17 males (mean age 53 years; range 32-77) (Table 1). The indications for the operation were urothelial tumours of the renal pelvis and/or ureter in 9 patients (Nos 1, 2, 3, 4, 5, 13, 16, 17, 20), recurrent stones of the upper urinary tract in 7 (Nos 10, 11, 12, 14, 15, 18, 19) and persisting outflow obstruction and pain after unsuccessful pyeloplasty in 4 (Nos 6, 7, 8, 9). The pre-operative IVU showed unimpaired outflow conditions in 8 of the 9 patients operated on for tumour; one patient (No. 20) had a minimal dilatation of the proximal ureter. Four of the 7 patients operated on for stones showed a slight dilatation of the collecting system; in 3 (Nos 10, 12, 18) the dilatation included the ureter and the calices, and in one (No. 11) the ureter alone. The conventional IVU showed no evidence of outflow obstruction in one post-pyeloplasty patient (No. 8), but clubbing of the calices was observed in the other 3 (Nos 6, 7, 9). Provocation with a diuresis increased dilatation in patients 7, 8 and 9. Patients 6 and 7 were drained with a percutaneous nephropyelostomy 22 and 58 days respectively before autotransplantation and, thus, before the renal function studies. Two stone patients have been excluded from the study (Nos 12

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Table 1 Pre-operative and Post-operative Serum Creatinine Values (µmol/l) in Patients Treated by Autotransplantation of the Kidney

Patient No.	*Age (years)*	*Sex*	*Pre-operative value*	*Value on day of discharge*	*Value 3 months post-operatively*
1	63	M	100	120	115
2	51	M	115	100	115
3	61	M	117	97	110
4	70	M	87	150	95
5	66	M	100	100	75
6	35	M	92	96	123
7	32	M	89	72	94
8	47	F	91	69	80
9	52	F	65	72	94
10	52	M	153	160	120
11	48	M	105	86	100
12*	61	M			
13	77	F	68	59	67
14*	35	M			
15	32	M	87	61	95
16	56	M	93	91	89
17	60	M	80	83	80
18	50	M	64	89	79
19	61	M	115	109	104
20	51	M	86	93	89
Mean ± SE	53 ± 3		95 ± 5	95 ± 6	96 ± 4

* Patients Nos 12 and 14 omitted because of kinking of the renal artery and graft loss respectively.

and 14); in one patient (No. 14) the blood supply to the kidney, which had previously undergone 2 partial nephrectomies *in situ*, was shown to be interrupted at post-operative angiography; at the subsequent exploration it was found that the renal vein had been twisted. The kidney of the other patient (No. 12) was explored the day after transplantation because of anuria; kinking of the renal artery was revealed and a new anastomosis was created to the external iliac artery; the vascular complication resulted in decreased function which is not representative of the preservation procedure.

Surgical technique Two separate incisions were employed. The kidney was exposed through a transverse, transperitoneal incision mobilising the ascending or descending colon. The renal artery and vein were dissected close to the aorta and the vena cava. The whole kidney was mobilised before the renal vessels were crossclamped and transected. The ureter and extrarenal portion of the renal pelvis were resected, leaving a brim large enough to permit an anastomosis to the urinary bladder. In the 9 patients with urothelial tumours the intrarenal collecting system was checked by means of a resectoscope for children (14 F). Any additional tumours were either excised and the calices reconstructed (No. 4) or coagulated on the bench (Nos 2, 3). Plain films of the five kidneys with recurrent stones were exposed to reveal calcifications which were removed. In the 4 patients with outflow obstruction no additional measures were taken on the bench. In 5 patients, 1 to 3 accessory arteries were simply anastomosed end-to-side to the main renal artery or conjoined side-to-side and thereafter anastomosed end-to-side to the main artery or end-to-end to the internal iliac artery. No accessory vessels were ligated. The kidney was implanted extraperitoneally in the ipsilateral iliac fossa through an oblique incision. It was placed with its long axis almost transversely, its upper pole laterally and its posterior surface anteriorly. The renal vein and artery were anastomosed end-to-side to the external iliac vein and artery using 6/0 Ticron (American Cyanamid) running sutures. After extensive mobilisation the urinary bladder was anastomosed to the renal pelvis using running 3/0 Dexon (American Cyanamid) sutures. The diameter of the anastomosis was 1 to 2 cm. The bladder was then hitched with a few interrupted stitches to the anterior renal capsule to relieve the tension in the anastomosis.

Preservation procedures Efforts were made to have the patient well hydrated at the onset of surgery by the administration of 1000 ml Ringer's solution the night before surgery. After introduction of the anaesthesia, a slow intravenous infusion of 500 ml 10% low molecular weight dextran solution (Rheomacrodex, Pharmacia) was started and continued for the next 24 h. Before clamping of the renal vessels, 200 ml of a 15% mannitol solution were given by rapid intravenous infusion. The kidney was immediately perfused through the artery with a mixture of 20 ml 0.5% lignocaine-hydrochloride (Xylocaine, Astra) and 0.5 ml heparin (5000 units per ml) at room temperature followed by flushing with Sacks' II solution (Sacks *et al.*, 1974) at +6°C by gravity from a height of 100 cm until the kidney was cool and pale and the venous effluent macroscopically bloodless. During the time on the bench the kidney was kept cold by perfusion with Sacks' solution and by being placed on a flat piece of ice covered with cloth. If the site for the transplantation had not yet been prepared, the kidney was stored in a refrigerator (+6°C) until used. The warm ischaemia time ranged between 1 and 5 min. The mean cold ischaemia time was 239 min (range 135-345). Immediately before recirculation the patient received another 200 ml of 15% mannitol by rapid i.v. infusion. The post-operative regimen included urinary bladder drainage by an indwelling urethral catheter for about 2 weeks, prophylaxis against thrombosis with Rheomacrodex 500 ml i.v. daily for 3 days and prophylactic antibiotics. During the first 3 days a diuresis of at least 100 ml/h was aimed at. Renal angiography was carried out on the eighth to the fourteenth day post-operatively.

Functional evaluation The patients were followed pre- and post-operatively during their stay in the ward with daily determinations of the serum concentration of creatinine. The GFR was studied with ^{51}Cr-EDTA clearance (Brochner-Mortensen, 1972). The separate function of each kidney was estimated by ^{131}I-Hippuran renography using an individualised background subtraction technique (Haugstvedt *et al.*, 1980). The influence of the preservation procedure on the proximal tubular function was studied by determination of the beta$_2$-microglobulin excretion in urine (Wibell, 1974). Distal tubular function was evaluated by testing the concentration ability after intranasal inhalation of desmopressin (Minirin, Ferring) (Delin *et al.*, 1978). The examinations were usually performed pre-operatively and repeated at the 3-month follow-up.

Renal angiography was performed both pre-operatively and post-operatively to check the integrity of the vascular tree. In patients with renal outflow obstruction, IVU during forced diuresis and retrograde pyelography was performed pre-operatively. The IVU during forced diuresis was then repeated at the 3-month follow-up. Bladder emptying was studied post-operatively with residual urine determination by catheterisation and urethrocystography including exposures during and after micturition. Bacterial cultures on urine were performed regularly.

Statistical methods Conventional statistical methods were used to calculate the mean and the standard error of the mean. The difference of matched pairs was tested by the Wilcoxon matched pairs signed ranks test and the correlation between matched pairs by the Spearman rank-correlation test.

Results

Post-operative angiography showed patent vascular anastomosis, including those of the accessory vessels, in the 18 patients. A slight stenosis of the renal artery was observed in one patient (No. 15) in whom the diameter of the renal artery decreased from 8 to 5 mm. The post-operative IVU, including examination during forced diuresis, showed unimpaired outflow conditions for the graft in all cases. Free communication with reflux of urine from the bladder to the graft was regularly observed at cystography. Mean residual urine amounted to 39 ± 11 ml. Three patients had significant bacteriuria at the 3-month follow-up but only one showed clinical symptoms (No. 2). Blood pressure remained unchanged post-operatively in all patients.

The mean pre-operative serum creatinine was 95 ± 5 μmol/l. The value was within normal limits in all patients except two; in one patient (No. 3) an insignificantly increased value of 117 μmol/l was registered, while one patient (No. 10), who had stones in a solitary kidney, displayed pre-operative serum creatinine values of about 153 μmol/l (Table 1). The mean serum creatinine value at the time of discharge was 95 ± 6 μmol/l; in 9 patients the values were lower than before autotransplantation (Nos 2, 3, 7, 8, 11, 13, 15, 16 and 19) and in one (No. 5) it was unchanged. At the 3-month follow-up the mean serum creatinine value was 96 ± 4 μmol/l. Even patient No. 10 displayed a value close to normal (120 μmol/l).

The mean total GFR pre-operatively was 84 ± 5 ml/min/1.73 m^2 BSA and at the 3-month examination 81 ± 5 ml/min (n.s.). The correspond-

Table 2 Glomerular Filtration Rate (ml/min/1.73 m^2BSA) Before and After Autotransplantation of the Kidney

Patient No.	*Total filtration rate* *Pre-operative*	*Post-operative*	*Graft filtration rate* *Pre-operative*	*Post-operative*	*Cold ischaemia time (min)*
1	61	53	61	53	180
2	68	68	34	34	345
3	68	84	28	34	210
4	86	62	43	31	240
5	67	66	25	27	205
6	72	89	23	y	225
7	111	106	52	50	155
8	x	(87)	x	y	
9	105	113	48	56	140
10	53	48	53	48	210
11	79	59	36	27	250
13	71	75	35	35	205
15	94	103	24	34	270
16	74	65	33	29	210
17	121	110	64	57	300
18	90	93	28	25	325
19	79	73	47	37	335
20	121	103	53	45	255
Mean ± SE	84 ± 5	81 ± 5	42 ± 3	39 ± 3	239 ± 15

x = Pre-operative GFR not determined. y = Post-operative radiorenography not performed.

There was no statistically significant change in total or graft GFR pre- and post-operatively. No statistically significant correlation existed between cold ischaemia time and change in graft GFR.

ing separate function of the graft was 42 ± 3 and 39 ± 3 ml/min, the difference not being significant. No correlation existed between cold ischaemia time and GFR (Table 2). When the patients with some degree of pre-operative outflow obstruction were omitted, the pre-operative split kidney GFR was 39 ± 5 ml/min and post-operatively it was 37 ± 3 ml/min (n.s.).

Proximal tubular function was normal in 10 patients examined both pre- and post-operatively and elevated values were not obtained in other patients either.

Distal tubular function was studied pre-operatively and 3 months post-operatively in 11 patients. The mean pre-operative osmolality was 638 ± 37 μmol/kg and post-operatively it was 645 ± 31 (Table 3). No correlation existed between cold ischaemia time and the change in concentration ability. When the patients with some degree of outflow obstruction were omitted, concentration ability in the remaining 5 patients was 619 ± 61 (SD) μmol/kg pre-operatively and 611 ± 100 (SD) μmol/kg post-operatively.

Table 3 Maximum Urinary Osmolality Before and After Autotransplantation of the Kidney

Patient No.	*Pre-operative value (μmol/kg)**	*Post-operative value (μmol/kg)**	*Cold ischaemia time (min)*
2	619	541	345
3	559	598	210
5	565	493	205
7	783	797	155
8	847	763	135
9	648	773	140
10	421	532	210
11	787	608	250
15	643	731	270
16	707	694	210
18	599	684	325
20	475	531	255
Mean ± SE	638 ± 37	645 ± 31	226 ± 19

* μmol/kg (= μOsm/kg)

There was no statistically significant change in concentration ability pre- and post-operatively. No statistically significant correlation existed between cold ischaemia time and change in concentration ability.

Discussion

This study has shown that it is feasible to remove a kidney, perform minor surgical bench procedures on it and retransplant it into the patient without measurable effects on glomerular or tubular function at follow-up 3 months later. The preservation programme in this series consisted of pre-treating the patient with mannitol and flushing the kidney with a Xylocaine-heparin solution followed by a cold Sacks' II solution.

In the 2 patients with a solitary kidney (Nos 1 and 10) the function of the graft could be determined directly in terms of both GFR and tubular function. In the patients with a contralateral kidney the situation was different and the separate function of the graft had to be estimated indirectly by dividing the total GFR by a split kidney function determination obtained by renography. This technique has been evaluated in children with varying renal disorders and found to be reliable (Granerus *et al.*, 1980). It may be argued that the measurement from a normally located kidney is not comparable with that from a transplanted kidney in the iliac fossa. However, the background subtraction method used does take this into consideration by correcting for background activity in a mode related to the amplitude of phase I of the renogram. This procedure, although simple and manual, seems sound as the phase I amplitude depends on the skin-kidney distance and the blood volume seen by the detector. Thus, after transplantation, renographic side distribution should offer a reasonably accurate estimate of graft function.

The total GFR of the two kidneys might be unrepresentative of the graft function post-operatively due to compensatory hypertrophy of the contralateral kidney. On the other hand, there is no reason to believe that the contralateral kidney could compensate completely or conceal an increased excretion of beta$_2$-microglobulin from the graft as well as a reduced concentration ability. The normal excretion of beta$_2$-microglobulin and unchanged concentration ability at follow-up support the GFR measurements and indicate unimpaired glomerular and tubular function of the transplant.

Most studies of the efficacy of various preservation methods used to maintain kidney function have been performed in animals (Sacks *et al.*, 1974; Pegg, 1978). In many of these studies one kidney has been taken out, preserved extracorporeally for a certain time and autotransplanted into the animal at the same time as contralateral nephrectomy is performed. In human allotransplantation the main obstacle to a detailed study of the preservation procedure is that it is not possible to eliminate immunological influences on the graft. This problem is inherent in the transplantation of kidneys from living and from cadaveric donors. When cadaveric kidneys are used other problems arise, *i.e.* the preceding renal function is not known and some kidneys have been subjected to warm ischaemia. In humans the efficacy of different kidney preservation methods must be studied in connection with bloodless renal surgery *in situ* (Wagenknecht *et al.*, 1977; Wickham *et al.*, 1979) or extracorporeally. *In situ*, however, the choice of the perfusate is limited as solutions with a high potassium content cannot be used. Most of the kidneys that have been autotransplanted so far have been subjected to extensive surgery, including the removal of parenchymatous tumours (Calne 1973; Brynger *et al.*, 1981; Novick *et al.*, 1981), multiple nephrotomies (Turini *et al.*, 1977; Pettersson *et al.*, 1981) and comprehensive vascular reconstruction (Belzer *et al.*, 1974; Blohmé *et al.*, 1981; Novick *et al.*, 1981). The introduction of direct pyelocystostomy has widened the indications for autotransplantation and kidneys with intact parenchyma and vessels are being transplanted. The present study has enabled us to conclude that autotransplantation of a kidney, including a cold ischaemia time of up to 345 min, can be accomplished without measurable effects on glomerular or tubular function.

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The Authors

T. Ranch, MD, Registrar.
H. Brynger, MD, PhD, Associate Professor of Surgery.
G. Granerus, MD, PhD, Associate Professor of Clinical Physiology.
Ch. Henriksson, MD, PhD, Associate Professor of Urology.
A. E. Nilson, MD, Chief Radiologist.
S. Pettersson, MD, PhD, Professor of Urology.

Requests for reprints to: S. Pettersson, Department of Urology, Sahlgrenska sjukhuset, S-413 45 Göteborg, Sweden.

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Immunohistological Detection of T Antigen and ABH Blood Group Antigens in Upper Urinary Tract Tumours

S. KAGAWA, H. TAKIGAWA, M. GHAZIZADEH and K. KUROKAWA

Department of Urology, University of Tokushima, Tokushima, Japan

Summary—The status of T antigen was assessed by means of peanut agglutinin (PNA) used in an immunoperoxidase technique, and the status of ABH blood group antigens was determined by the specific red cell adherence (SRCA) test. Thirty-eight patients with upper urinary tract tumours were examined.

Our data indicated that T antigen status did not correlate with conventional prognostic indicators such as grade and stage of tumour and survival of patients, while the expression or deletion of ABH blood group antigens did correlate well.

It was concluded that ABH blood group antigen determination might provide a useful prognostic probe in upper urinary tract tumours should it find clinical application.

Peanut agglutinin (PNA) is known to bind β-D-galactosyl(1-3)-N-acetyl-D-galactosamine, which is the major antigenic determinant of Thomsen-Friedenreich antigen. This antigen is thought to represent a precursor of the human blood group MN system (Lotan *et al.*, 1975; Springer *et al.*, 1979).

In the tissue sections, peanut agglutinin may be used in immunohistochemical techniques to detect the antigenic determinants. These are identical to the so-called T antigen and are referred to as such in this report. In normal urothelium, T antigen is in the cryptic form and it can be demonstrated after neuramidase digestion (Alroy *et al.*, 1982). Several studies have shown the expression of T antigen in transitional cell carcinoma of the bladder as well as malignant lesions of other organs (Newman *et al.*, 1979; Coon *et al.*, 1982; Lehman et al., 1984).

On the other hand, deletion or expression of ABH blood group antigens has proved to be a useful prognostic indicator of transitional cell carcinoma of the bladder (Decenzo *et al.*, 1975; Lange *et al.*, 1978; Emmott *et al.*, 1979; Limas *et al.*, 1979; Johnson and Lamm, 1980; Richie *et al.*, 1980).

The purpose of this study was to analyse the expression of T antigen in various grades and stages of transitional cell carcinoma of the upper urinary tract and to compare the status of T antigen with ABH blood group antigens in these tumours.

Material and Methods

We examined tumour specimens from 38 patients with transitional cell carcinoma of the upper urinary tract for T antigen and ABH blood group antigens. The tissues had been fixed in buffered formalin solution and embedded in paraffin by standard techniques. There were 35 males and three females aged from 35 to 85 years (mean 64), with a mean follow-up period of 50 months. The tumours involved the renal pelvis in 18, the ureter in 11 and the renal pelvis and ureter in nine cases. Blood groups were identified from hospital records as follows: group A (13 patients); group B (10); group AB (4) and group O (11). Haematoxylin and eosin-stained sections of the lesions were reviewed to verify the grade. Tumours were classified as well, moderately and poorly differentiated for grades I, II and III respectively. The staging was done according to a modification of the Armed Forces

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Institute of Pathology classification: stage O—*in situ* carcinoma (Tis); stage I—tumour limited to mucosa (Ta); stage II—submucosal infiltration (T1); stage III—muscular invasion (T2, T3a); stage IV—involvement of adventitia, adjacent tissue (T3b, T4) and/or metastasis (M1). Eight patients had stage I, 17 stage II, 11 stage III and 2 stage IV disease.

Detection of T antigen and ABH blood group antigens was accomplished using an unlabelled lectin-anti-lectin immunoperoxidase technique and the specific red cell adherence test (SRCA) respectively. The techniques have been described previously by Ghazizadeh *et al.* (1982) and Coon *et al.* (1982). The individual sections were classified as antigen positive or negative.

SRCA test Positive results were defined as 30% or more of the area showing red cell adherence. Reagent controls included incubating the slide with non-isologous antibody and isologous erythrocytes. The endothelium of vessels and intrinsic erythrocytes in the section showed red cell adherence and served as positive controls. Mesenchymally derived cells do not have this antigen on their cell surface and served as built-in negative controls.

T antigen Tissue sections were recorded as positive for T antigen if more than 10% of the epithelium showed specific brown staining. In sections predigested with neuraminidase a rate exceeding 20% was considered positive. Controls included (a) abolition of specific staining for T antigen by omission of the peanut agglutinin or addition of 0.1 mole galactose to its diluent, and (b) intrinsic controls in tissue sections digested with neuraminidase, *i.e.* positive staining of erythrocytes plus vascular endothelium and negative staining of the stroma.

Survival rates were calculated by Kaplan-Meier's method and statistical differences were analysed by the Cox-Mantel test (Kaplan and Meier, 1958).

Results

T Antigen

Thirteen of the 38 upper urinary tract tumours (34%) were positive and 22 (58%) were negative for T antigen but demonstrated the presence of normal cryptic T antigen and 3 (8%) were negative for cryptic T antigen. Of 8 grade I, 18 grade II and 12 grade III tumours, 2 (25%), 7 (39%) and 7 (58%), respectively, were positive for T antigen or negative for T and cryptic T antigens. Six grade I (75%), 11 grade II (61%) and 5 grade III (42%) tumours were negative for T antigen but demonstrated the presence of normal cryptic T antigen after neuraminidase digestion (Table 1).

Table 1 Grade *vs* T Antigen

	T[−] *Cryptic T*[+] (%)	*T*[+] (%)	*T*[−] *Cryptic T*[−] (%)
Grade 1	6/8 (75.0)	0/8 (0)	2/8 (25.0)
Grade 2	11/18 (61.1)	7/18 (38.9)	0/18 (0)
Grade 3	5/12 (41.7)	6/12 (50.0)	1/12 (8.3)
Total	22/38 (57.9)	13/38 (34.2)	3/38 (7.9)

Of 25 low stage (I, II) and 13 high stage (III, IV) tumours, 10 (40%) and 6 (46%), respectively, were positive for T antigen or negative for T and cryptic T antigens (Table 2). Fifteen low stage (60%) and seven high stage (54%) tumours were negative for T antigen but demonstrated the presence of normal cryptic T antigen after neuraminidase digestion.

Table 2 Stage *vs* T Antigen

	T[−] *Cryptic T*[+] (%)	*T*[+] (%)	*T*[−] *Cryptic T*[−] (%)
Low stage	15/25 (60.0)	8/25 (32.0)	2/25 (8.0)
High stage	7/13 (53.8)	5/13 (38.5)	1/13 (7.7)
Total	22/38 (57.9)	13/38 (34.2)	3/38 (7.9)

Generally, the survival rate of the patients was proportional to the tumour grade and stage (Figs 1 and 2). Changes in the status of T antigen did not correlate with survival (Fig. 3).

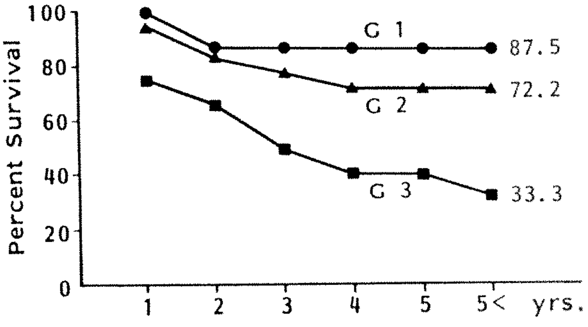

Fig. 1 Survival rate *vs* grade.

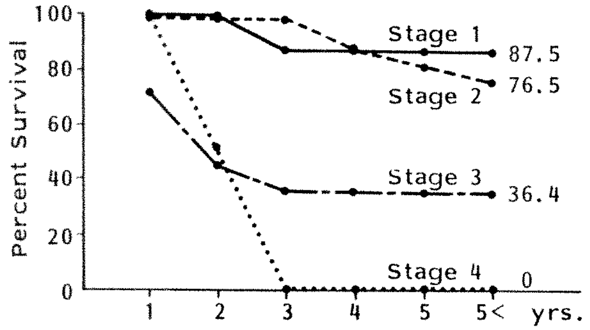

Fig. 2 Survival rate *vs* stage.

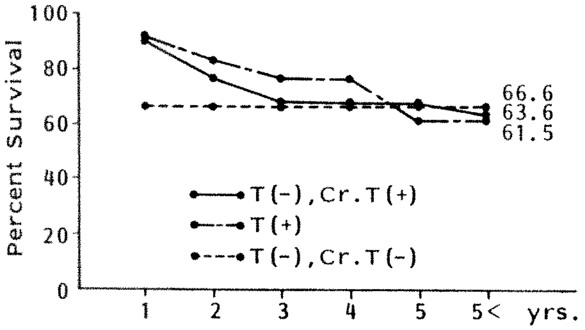

Fig. 3 Survival rate *vs* T antigen.

ABH Antigens

Eighteen of the 38 upper urinary tract tumours (47%) were positive and 20 (53%) were negative for ABH antigens (Table 3). Six of eight patients (75%) with grade I tumour had positive and 8 of 12 patients (67%) with grade III tumours had negative tests. In grade II tumours there was no marked difference between the positive and negative rate.

Table 3 Grade *vs* SRCA Test

	Positive (%)	*Negative* (%)
Grade 1	6/8 (75.0)	2/8 (25.0)
Grade 2	8/18 (44.4)	10/18 (55.6)
Grade 3	4/12 (33.3)	8/12 (66.7)
Total	18/38 (47.4)	20/38 (52.6)

Sixteen of 25 low stage (I, II) tumours (64%) were positive and 11 of 13 high stage (III, IV) tumours (85%) were negative for ABH antigens (Table 4).

Table 4 Stage *vs* SRCA Test

	Positive (%)	*Negative* (%)
Low stage	16/25 (64.0)	9/25 (36.0)
High stage	2/13 (15.4)	11/13 (84.6)
Total	18/38 (47.4)	20/38 (52.6)

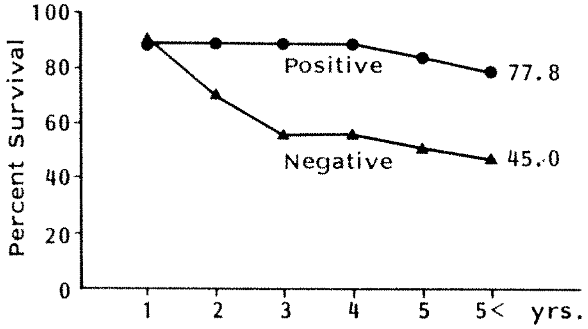

Fig. 4 Survival rate *vs* ABH antigen.

Overall, patients with antigen-positive tumours showed a significantly elevated survival rate compared with patients with antigen-negative tumours (Fig. 4).

The expression of T antigen was independent of the ABH blood group antigens.

Discussion

Several studies have shown the usefulness of ABH blood group antigen detection in predicting the prognosis of bladder cancer. The presence of these antigens on tumour cells indicates non-aggressive behaviour for the tumour, while their absence suggests a high risk of invasiveness. On the other hand, recent studies have shown the expression of T antigen in transitional cell carcinomas of the bladder as well as malignant lesions of other organs. Furthermore, a positive correlation has been demonstrated between T antigen status and histological grade as well as tumour invasion and recurrences in bladder cancer. Coon *et al.* (1982) found that 32% of low grade (I, II) and 95.2% of high grade (III) tumours were T antigen-positive or T and cryptic T antigen-negative. Low grade tumours which were cryptic T positive had a significantly lower incidence of invasion and recurrence compared with those which were cryptic T negative or T positive (49% *vs* 100%).

Our findings on analysis of T antigen and ABH blood group antigens in transitional cell carcinoma of the upper urinary tract revealed that changes in the status of T antigen were not useful prognostic indicators as they did not correlate with the conventional prognostic indicators such as tumour grade, stage and survival of patients. This contrasted with the findings of previous investigators, who had found a good correlation in transitional cell carcinoma of the bladder. However, ABH blood group antigen expression or deletion was found to correlate with tumour grade, stage and survival, thereby providing a useful prognostic probe should it find clinical application.

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The Authors

S. Kagawa, MD, Assistant Professor of Urology.
H. Takigawa, MD, Urologist.
M. Ghazizadeh, MD, Fellow in Urology.
K. Kurokawa, MD, Professor of Urology.

Requests for reprints to: S. Kagawa, Department of Urology, School of Medicine, The University of Tokushima, Tokushima 770, Japan.

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Prostaglandin Synthetase Inhibition of Renal Pelvic Smooth Muscle in the Rabbit

S. LUNDSTAM, O. JONSSON, B. KIHL and S. PETTERSSON

Department of Urology, Sahlgrenska sjukhuset, University of Göteborg, Göteborg, Sweden

Summary—The prostaglandin synthetase inhibitors diclofenac and indomethacin relieve pain in renal colic probably by decreasing renal pelvic pressure. Decreased diuresis and effects on the oedema around the obstructing stone are plausible explanations. In the present study on rabbit renal pelvic tissue strips it was found that both indomethacin and diclofenac decreased the spontaneous phasic activity of the strips. ED_{50} was $5.4 \pm 0.7 \times 10^{-5}$ M for indomethacin and $2.4 \pm 0.5 \times 10^{-5}$ M for diclofenac ($P < 0.001$). With the prostaglandin synthetase inhibitors still in the tissue bath the activity was regained when either prostaglandin E_2 or $F_{2\alpha}$ was added, prostaglandin E_2 being more potent in this respect. It was concluded that protaglandin synthetase inhibitors seem to reduce smooth muscle activity in the renal pelvis, a mechanism which might contribute to the pain-relieving ability of these drugs in renal colic.

Renal colic is caused by increased pressure and wall tension in the renal pelvis above the obstructing stone (Kiil, 1957). The pressure is dependent upon the diuresis, the ureteropelvic smooth muscle tone and the degree of obstruction. Increased pressure in the renal pelvis will induce synthesis and secretion of prostaglandins which increase renal blood flow and counteract the effect of the antidiuretic hormone (Orloff *et al.*, 1978; Morrison, 1980). Both of these effects increase the diuresis and raise the pressure further. Prostaglandins are also involved in the development of the inflammatory oedema around the stone. Prostaglandin synthetase inhibition by diclofenac or indomethacin probably relieves the pain in renal colic by decreasing the renal pelvic pressure (Holmlund and Sjödin, 1978; Lundstam *et al.*, 1982). Decreased diuresis and decreased oedema around the obstructing stone are plausible explanations (Sjödin, 1981). Another contributory factor might be a direct effect on the ureteropelvic smooth muscle tone. The present study was designed to evaluate the effect of prostaglandin synthetase inhibition on renal pelvic smooth muscle activity.

Material and Methods

Rabbits weighing 2 to 4 kg were used in the study. They were deprived of food for 12 h before the operation but had free access to water. Anaesthesia was induced by intramuscular administration of 0.5 ml/kg body weight of a mixture containing phentanyl citrate 0.315 mg/ml and fluanisone 10 mg/ml (Hypnorm Vet, Leo, Sweden). Spontaneous respiration of room air was preserved throughout the operation. A long midline incision was performed and the kidneys were gently exposed. Bilateral nephrectomy was performed and care was taken not to stretch the ureters. The intrarenally located renal pelves were dissected free by dividing the renal parenchyma. One tissue strip from each renal pelvis (measuring approximately 2-3 × 5-10 mm) was prepared. The strips were mounted in a tissue bath with oxygenated Krebs' solution (NaCl 122, KCl 4.73, $CaCl_2$ 2.49, $MgCl_2$ 1.19, $NaHCO_3$ 15.5, KH_2PO_4 1.19 and glucose 11.5 mmol/l) at 37°C. The spontaneous phasic activity of the strips was recorded isometrically with a force displacement transducer (Grass FT 03) and recorded on a Grass Polygraph (Fig. 1). The passive tension was adjusted to 500 dyn. Diclofenac (Voltaren, Ciba Geigy, Sweden), indomethacin

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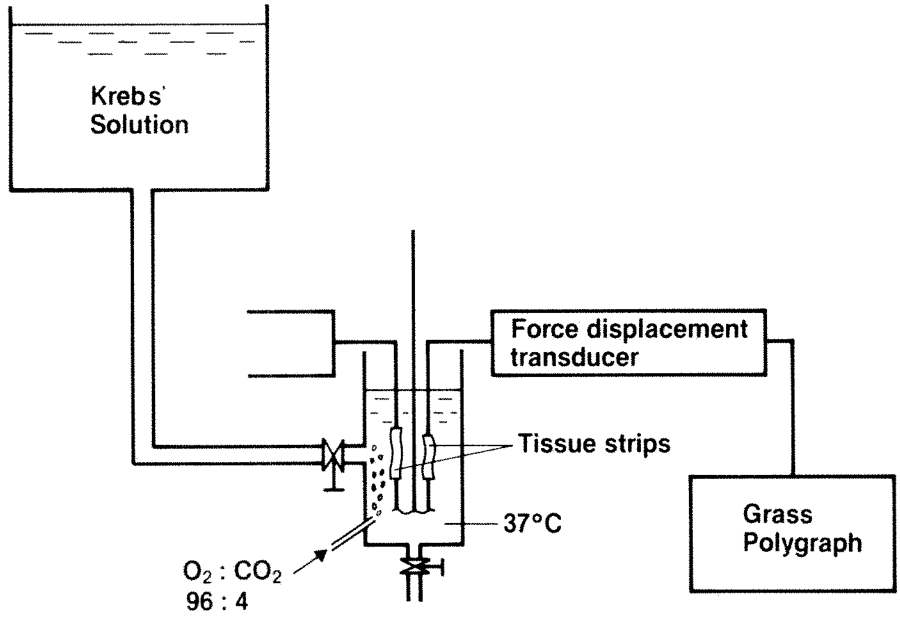

Fig. 1 Experimental design.

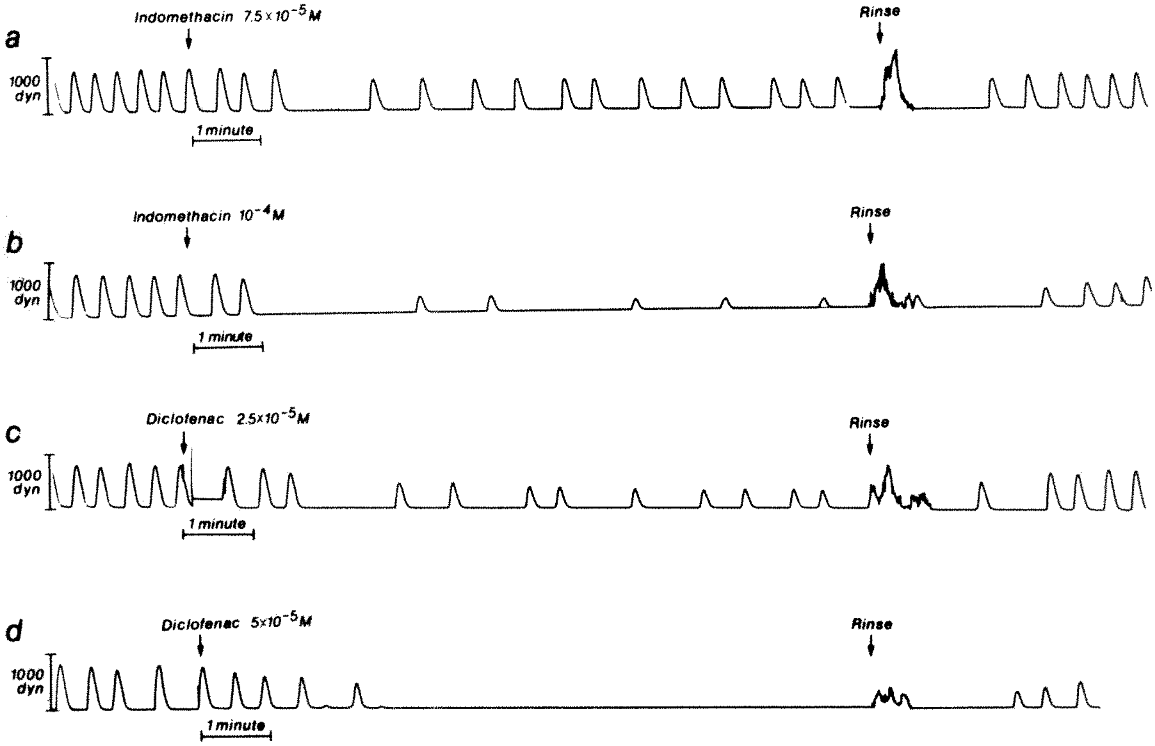

Fig. 2 Spontaneous phasic activity of a representative renal pelvic strip and the effect of diclofenac and indomethacin.
(a) Indomethacin (7.5×10^{-5} M) decreased the amplitude and frequency of the contractions.
(b) Indomethacin (10^{-4} M) almost eliminated all smooth muscle activity.
(c) Diclofenac (2.5×10^{-5} M) decreased the amplitude and frequency of the contractions.
(d) Diclofenac (5×10^{-5} M) eliminated smooth muscle activity.

(Confortid, Dumex, Sweden), prostaglandin E_2 or $F_{2\alpha}$ (purchased from Sigma Chemical Co., USA) were added to the bath in concentrations given in the Results section. To obtain dose response curves the effect of diclofenac and indomethacin was registered for a 10-min period and the strips were then rinsed four times with fresh, pre-warmed, oxygenated Krebs' solution. After an accommodation period of 10 to 15 mins further dosages of the substances were added. Indomethacin was studied as the first substance in half of the experiments and diclofenac in the other half. The phasic activity was quantified by calculating the surface below the registration of the mechanical activity with an electronic plotter. The effects of the drugs were calculated as the ratio integrated surface between the 8 to 10 min of exposure and the integrated surface during 2 min immediately before exposure. Dose-response curves and ED_{50} values were calculated by computer technique for each tissue strip from a series of exposures to different concentrations.

In one series of experiments either PGE_2 or $PGF_{2\alpha}$ was added to previously untreated strips and in another to strips treated with diclofenac or indomethacin without rinsing out the prostaglandin synthetase inhibitor from the bath.

Results

Twenty tissue strips exhibiting spontaneous activity were studied. The smooth muscle contractions were small initially but after an accommodation period of up to 30 min, regular contractions of 200 to 1000 dynes were achieved with a frequency of 2 to 5 min. After the accommodation period, when the phasic activity was regular, the different compounds were added to the bath.

The addition of prostaglandin E_2 or $F_{2\alpha}$ at a final concentration of 10^{-7} to 10^{-6} M caused no major changes in the muscle activity in 7 of 7 strips.

Both diclofenac and indomethacin reduced the amplitude and frequency of the concentrations (Fig. 2). This reduction was dependent on the dose and at a concentration of diclofenac of $0.5\text{-}2 \times 10^{-4}$ M and indomethacin of $1\text{-}4 \times 10^{-4}$ M all smooth muscle activity was eliminated. Inhibition of the phasic activity was more pronounced at equimolar concentrations of diclofenac (Fig 3). ED_{50} was $5.4 \pm 0.7 \times 10^{-5}$ (mean ± SE, n = 8) for indomethacin and $2.4 \pm 0.5 \times 10^{-5}$ (mean ± SE, n = 8) for diclofenac ($P < 0.001$). Spontaneous activity was always regained after rinsing with fresh Krebs' solution. Smooth muscle activity was also fully regained when prostaglandin E_2 was added at a concentration of 10^{-7} to 10^{-6} M to the bath still containing diclofenac or indomethacin (Fig. 4). Prostaglandin $F_{2\alpha}$ was less potent in this respect and a concentration of $1\text{-}2 \times 10^{-6}$ M was needed to partly regain the muscle activity.

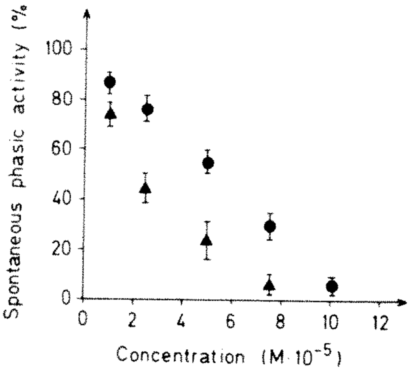

Fig. 3 Inhibition of renal pelvic smooth muscle activity by diclofenac (▲, mean ± SE, n = 8) or indomethacin (●, mean ± SE, n = 8).

Discussion

The pain-relieving ability of the prostaglandin synthetase inhibitors diclofenac and indomethacin in renal colic has been ascribed to the decrease in renal blood flow and diuresis caused by these drugs (Sjödin, 1981). The possible effects of prostaglandin synthetase inhibitors on ureteropelvic smooth muscle activity have not been studied previously. Abrams and Feneley (1976) investigated the effect of prostaglandins on isolated human ureteric preparations and found that prostaglandin E_1 and E_2 seemed to reduce spontaneous activity, whereas $PGF_{2\alpha}$ increased it. Boyarsky *et al.* (1966) demonstrated an inhibitory effect of PGE_1 on the contractility of ureters from the dog. In the present study no major changes in spontaneous smooth muscle activity were found when either prostaglandin PGE_2 or $PGF_{2\alpha}$ was added to the tissue bath. The reason for this might be that the muscle preparations were already stimulated by endogenous prostaglandins. The inhibitory effect of both indomethacin and diclofenac, two chemically different prostaglandin synthethase inhibitors, points to that explanation. When the concentrations of indomethacin or diclofenac in the bath were increased the contractions decreased and were finally eliminated. ED_{50} was significantly higher for indomethacin (5.4×10^{-5} M) than for diclofenac (2.4×10^{-5} M). In experiments with diclofenac or indomethacin still in the bath the muscle activity

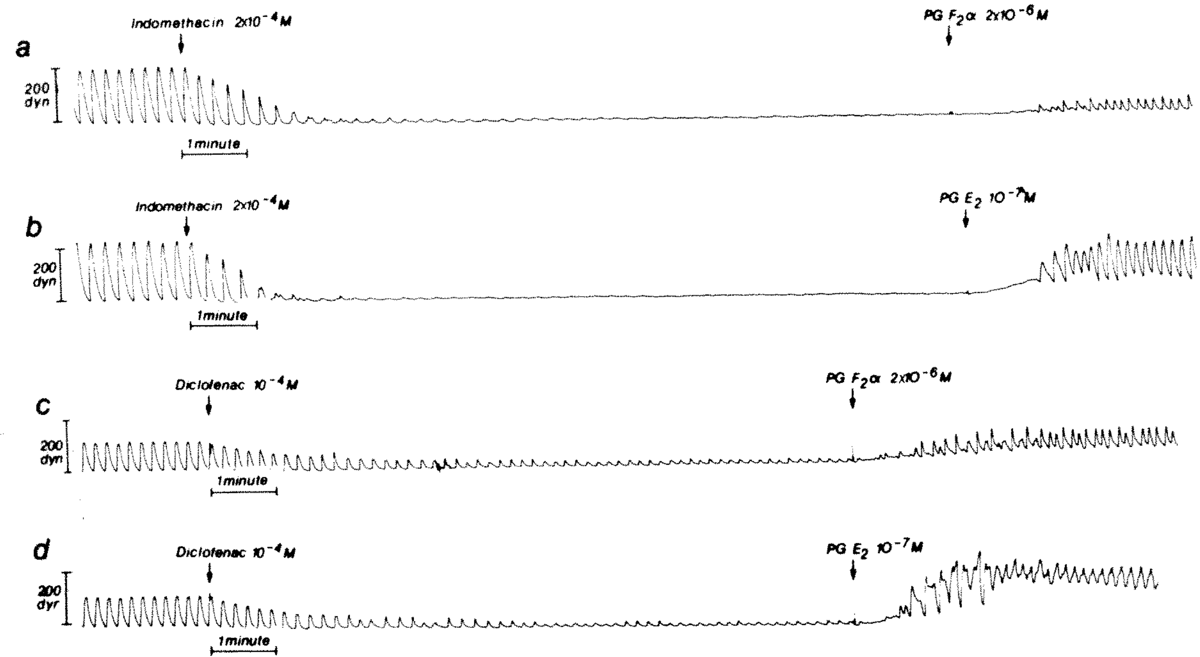

Fig. 4 The effect of $PGF_{2\alpha}$ and PGE_2 on a representative renal pelvic strip after prostaglandin synthetase inhibition.
(a-b) Indomethacin (2×10^{-4} M) eliminated all smooth muscle activity. $PGF_{2\alpha}$ (2×10^{-6} M) caused weak smooth muscle activity and PGE_2 (10^{-7} M) caused strong smooth muscle activity.
(c-d) Diclofenac (10^{-4} M) almost eliminated smooth muscle activity. $PGF_{2\alpha}$ (2×10^{-6} M) caused weak muscle contractions while PGE_2 (10^{-7} M) caused strong muscle activity.

could be regained by adding prostaglandin E_2 or $F_{2\alpha}$. PGE_2 was much more potent than $PGF_{2\alpha}$. Other prostaglandins may also be involved with inhibitory or stimulative effects. However, the net effect of prostaglandins on renal pelvic smooth muscle seems to be stimulative, since diclofenac and indomethacin, which both inhibit the transformation of arachidonic acid into prostaglandins, inhibit muscle activity. Irrespective of the mechanism, prostaglandin synthetase inhibitors seem to reduce smooth muscle activity in the renal pelvis, which might contribute to the pain-relieving ability of these drugs in renal colic.

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The Authors

S. Lundstam, MD, PhD, Associate Professor of Surgery.
O. Jonsson, MD, PhD, Associate Professor of Surgery.
B. Kihl, MD, PhD, Associate Professor of Urology.
S. Pettersson, MD, PhD, Professor of Urology.

Requests for reprints to: S. Lundstam, Department of Urology, Sahlgrenska sjukhuset, S-413 45 Göteborg, Sweden.

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Malignant Phaeochromocytoma

H. J. E. LEWI, R. REID, B. MUCCI, J. K. DAVIDSON, K. F. KYLE, S. G. MACPHERSON, P. SEMPLE
and S. KAYE

Departments of Urology, Radiology and Pathology, University Department of Surgery and MRC Blood Pressure Unit, Western Infirmary; University Department of Oncology, Gartnavel General Hospital, Glasgow

Summary—Malignant phaeochromocytoma is a rare tumour and experience in its management is therefore limited. Five patients are discussed in whom the development of metastases was associated with rapidly progressive disease.

Malignant phaeochromocytoma is an uncommon tumour which accounts for less than 20% of all cases of phaeochromocytoma (Remine *et al.*, 1974; Modlin *et al.*, 1979; Van Heerden *et al.*, 1982). Malignant behaviour is difficult to predict from histological appearances, as the presence of metastases is the only acceptable criterion (Shapiro *et al.*, 1984). Management is based primarily on surgical resection and the relief of symptoms by catecholamine blockade (Modlin *et al.*, 1979; Brennan and Keiser, 1982; Van Heerden *et al.*, 1982), with the addition of radiotherapy to treat painful bony metastases (James *et al.*, 1972). Control of metastatic spread is difficult and the results of chemotherapy have been disappointing (Brennan and Keiser, 1982). Because of the rarity of the tumour, experience in the management of metastatic disease is limited.

Five patients are presented in whom the development of metastases was associated with rapidly progressive disease.

Patients

Case 1 (MM) A 53-year-old female presented with a pathological fracture of the right femur. Biopsy showed infiltration by metastatic tumour possibly of renal origin.

Following femoral fixation the blood pressure remained elevated at 200/110 and the urinary normetadrenalin was raised at 34 μmol/24 h. Plain radiographs and intravenous urography (IVU) showed a calcified mass in the suprarenal area. Arteriography, including selective catheterisation of the left middle adrenal artery, demonstrated a predominantly avascular tumour of the left adrenal gland (Fig. 1) and the isotope bone scan demonstrated raised uptake suggestive of metastases in the thoracolumbar spine. Under combined $\alpha + \beta$ adrenergic blockade, laparotomy was carried out; an unresectable adrenal tumour was found, together with three metastatic deposits in the liver. Liver biopsy confirmed metastatic phaeochromocytoma. Despite successful control of hypertension and pain relief, the patient's condition deteriorated and she died 15 months following presentation.

Case 2 (FH) A 51-year-old female presented with a 2-year history of diarrhoea and abdominal pain; abdominal ultrasound demonstrated a right adrenal mass and arteriography revealed a vascular tumour of the right adrenal gland. Both urinary and plasma catecholamine levels were normal and the patient remained normotensive. At laparotomy a well circumscribed adrenal tumour was removed. The histological appearances were those of a spindle cell phaeochromocytoma composed of fascicles of spindle-shaped cells with nuclear pleomorphism and a granular cytoplasm (Fig. 2). Electron microscopy demonstrated electron-dense membrane-bound neurosecretory granules.

For 10 years the patient remained asymptomatic and normotensive, with normal plasma and urinary catecholamines, but subsequently developed persistent right upper quadrant abdominal pain and intermittent jaundice due to gall-stones. At laparotomy extensive metastases were found in the liver, omentum and diaphragm. Biopsy confirmed metastatic spindle cell phaeochromocytoma.

The patient received 6 cycles of 5-fluorouracil (5 FU) and streptozotocin and remained well for 32 months, but then developed enlarging masses in the right iliac and left supraclavicular fossae. During 3 months' treatment with chlorambucil there was shrinkage of the supraclavicular

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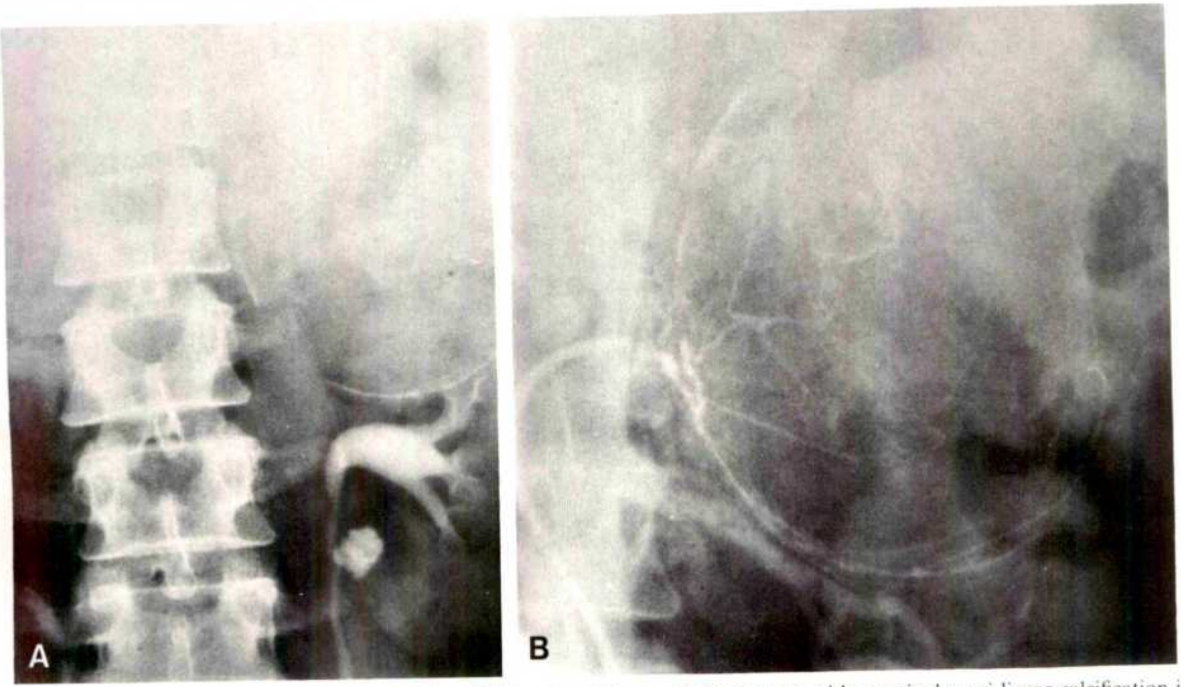

Fig. 1 (*Case 1*) (A) Ten-minute radiograph from IVU series. A large soft tissue mass with marginal curvi-linear calcification is situated above the left kidney. The kidney is displaced inferiorly. (B) Selective arteriogram of left middle adrenal artery shows circulation around the left suprarenal tumour demonstrated in Figure 1A. The tumour itself is relatively avascular.

fossa but no change in the abdominal mass. The disease was stabilised for 4 months, but in the last 2 months there has been escape of disease control with further growth of the palpable metastatic deposits.

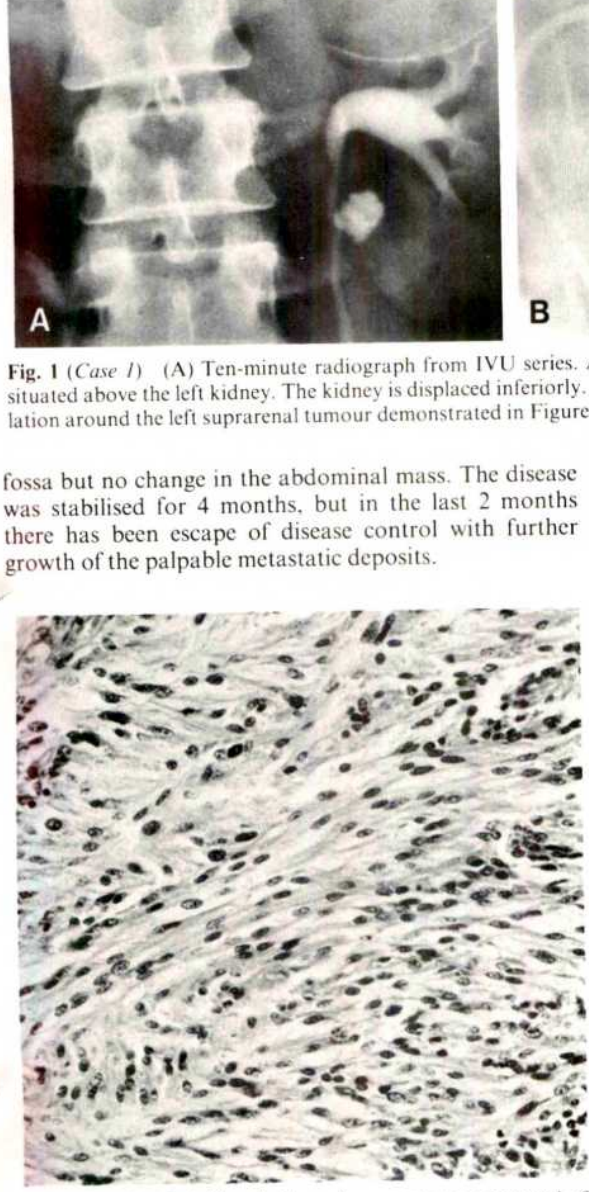

Fig. 2 (*Case 2*) Spindle cell phaeochromocytoma composed of fasicles of spindle shaped cells with mild nuclear pleomorphism and granular cytoplasm. (H and E, original magnification × 160).

Case 3 (*MW*) A 29-year-old female presented with a 6-month history of back pain. Plain radiography demonstrated collapse of the seventh thoracic vertebra. Needle biopsy showed metastatic tumour composed of groups of cells with an eosinophilic granular cytoplasm. IVU revealed a suprarenal mass compressing the left kidney and ultrasound showed that the mass was composed of a mixture of echo-free and echogenic areas, thought to represent regions of cystic necrosis and haemorrhage (Fig. 3). Isotope scans (bone and liver) showed increased

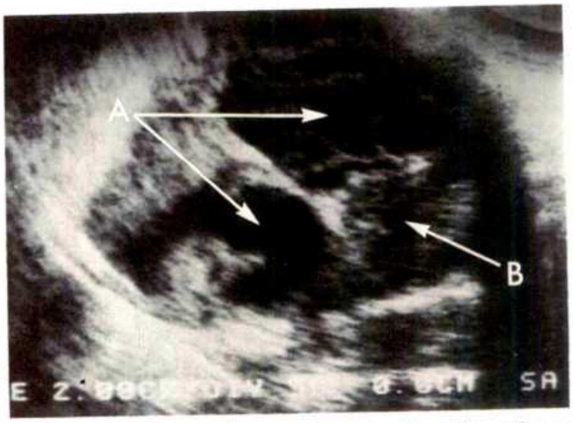

Fig. 3 (*Case 3*) Prone ultrasound examination of the left renal area. There is a well defined mass (A) above the upper pole of the kidney (B). There are multiple echo-free areas within the mass representing areas of cystic necrosis.

uptake suggestive of metastases, including the left parietal region of the skull, the left tenth rib and liver. Urinary normetadrenalin was elevated at 73.3 μmol/l and serum noradrenalin was also elevated at 29 μmol/l. Because of the patient's anxiety state and tachycardia, α and β adrenergic blockade therapy was commenced (phenoxybenzamine plus propanolol). Biopsy of the left tenth rib confirmed metastatic phaeochromocytoma which histologically had appearances identical to those of the original needle biopsy. Electron microscopy demonstrated membrane-bound, electron-dense neurosecretory granules (Fig. 4).

In view of the widespread nature of the disease the patient was given combination chemotherapy (cyclophosphamide, Adriamycin, vincristine and prednisolone). After 3 cycles the cyclophosphamide was withdrawn and streptozotocin introduced. Despite this therapy there has been progression of disease with a persistently elevated serum noradrenalin.

Case 4 (*ED*) A 20-year-old female presented with blurring of vision and was found to have papilloedema, hypertension (190/140) and a palpable abdominal mass. Isotope liver scan showed compression of the right lobe by an extrinsic mass and CT scan demonstrated a suprarenal mass displacing the right kidney and liver (Fig. 5). Isotope bone scan showed metastases in the right ninth and tenth ribs; serum noradrenalin was elevated (> 80 μmol/l) and serum adrenalin was normal.

At laporotomy (under α and β adrenergic blockade) a large inoperable tumour was found to be invading the right kidney, liver, inferior vena cava and retroperitoneal tissue. A supraduodenal lymph node biopsy showed the histological features of a phaeochromocytoma and electron microscopy demonstrated electron-dense, membrane-bound neurosecretory granules.

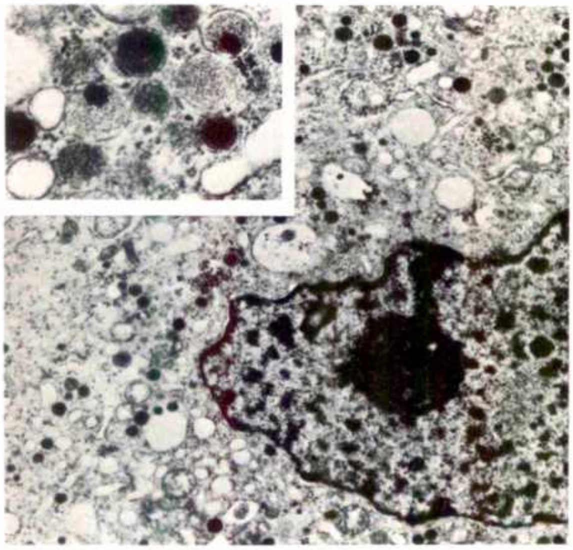

Fig. 4 (*Case 3*) Electron micrograph showing numerous electron-dense secretory granules throughout the cytoplasm. (× 8500). Insert shows the dense membrane-bound granules. (× 32,000).

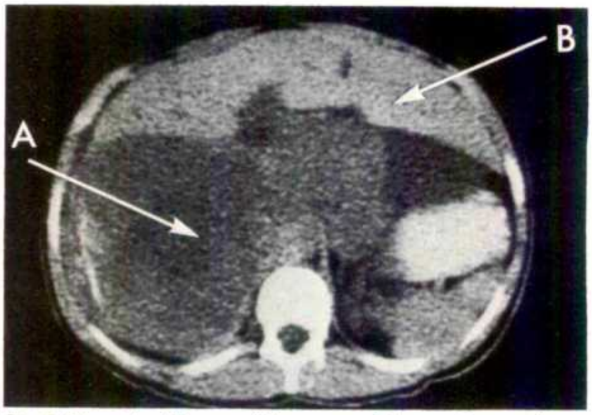

Fig. 5 (*Case 4*) CT scan of the upper abdomen shows a large well defined mass in the right suprarenal area (A) with displacement of the liver (B).

The patient was given combination chemotherapy (Adriamycin, vincristine and cyclophosphamide) and this stabilised the disease for 4 months. She subsequently developed ascites and a mass in the left supraclavicular fossa. Cyclophophamide therapy was instituted, with little effect, over a 2-month period. Interferon was introduced in the hope of promoting differentiation but the patient died of progressive disease 1 month later.

Case 5 (*MC*) A 29-year-old female was investigated for persistent hypertension, following her third pregnancy, and recent onset of blurred vision. Blood pressure was elevated at 230/160 and she had a persistent tachycardia (120/min). Both urinary normetadrenalin (34.8 μmol/24h) and VMA (113/24h) were elevated. Ultrasound demonstrated a mass below the right kidney, confirmed by arteriography.

Alpha and β adrenergic blockade was given for control of hypertension and at laparotomy a large tumour was removed from the right para-aortic region below the level of the right renal artery. The histological features were those of a highly vascular phaeochromocytoma with the cells arranged in an alveolar pattern (Fig. 6). Post-operatively the urinary normetadrenalin fell to normal, the blood pressure to 160/115 and the pulse became normal.

Ten months later a mass appeared in the left supraclavicular fossa and abdominal ultrasound showed a large retroperitoneal recurrence. The supraclavicular mass was excised and was found to have histological appearances identical to those of the original tumour. The patient remained asymptomatic for a further 14 months, when the supraclavicular mass recurred and was again excised. A chest radiograph demonstrated multiple pulmonary metastases and she rapidly developed a palpable abdominal mass, hypertension, sweating and a painful osteolytic deposit in the seventh cervical vertebra.

Radiotherapy was given to the spine, and α methyltyrosine (a noradrenaline inhibitor) was given to control

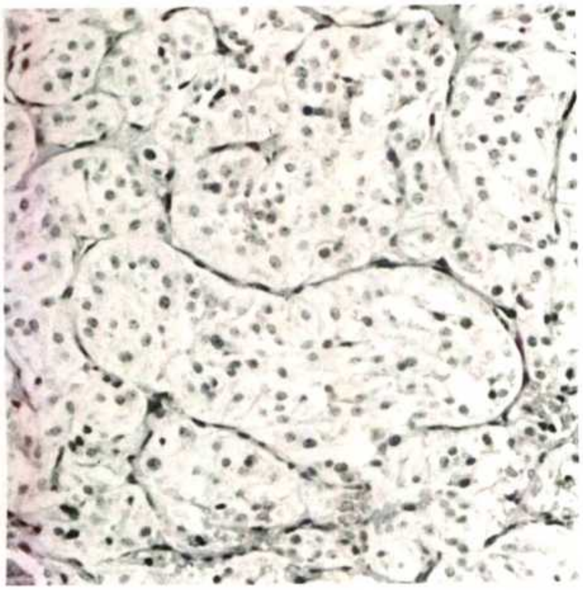

Fig. 6 (*Case 5*) Phaeochromocytoma arranged in alveolar pattern with a prominent capillary network. (H and E, original magnification × 160).

the adrenergic symptoms. Her subsequent course was complicated by severe constipation, atonic megacolon and small bowel distension. This was treated initially by a transverse colostomy and subsequently by total colectomy and ileostomy. At laparotomy an extensive retroperitoneal tumour was noted. The patient's condition continued to deteriorate and she died 3 months following colectomy. At post-morten, extensive metastatic disease was noted in the retroperitoneum, lung and bony skeleton.

Discussion

All five patients were female, in the age range 20 to 53 years. Metastases were present at the time of diagnosis in three cases and the remaining two patients developed metastases 10 months and 10 years following presentation. In all cases the development of metastases was associated with rapid progression of disease and three patients died within 42 months of presentation.

Malignant phaeochromocytoma is an uncommon tumour, with less than five cases arising annually in the United Kingdom. Between 8 and 19% of all phaeochromocytomas are malignant, extra-adrenal tumours being more commonly malignant than the primary adrenal phaeochromocytomas (Remine *et al.*, 1974; Mahoney and Harrison, 1977; Modlin *et al.*, 1979; Scott *et al.*, 1982; Van Heerden *et al.*, 1982).

The biological behaviour of the tumour is difficult to predict, for in the absence of proven metastatic disease the aggressive nature of the primary tumour cannot be determined by histological appearances (Young and Karmi, 1978; Modlin *et al.*, 1979; Shapiro *et al.*, 1984). The true definition of a malignant phaeochromocytoma is one in which metastases are present at a site where chromaffin tissue is not otherwise found, thus excluding cases of multifocal and recurrent phaeochromocytoma (Shapiro *et al.*, 1984).

Local recurrence is well recognised and may be related to the presence of an unrecognised multicentric tumour, incomplete resection or tumour spillage at operation (Brennan and Keiser, 1982). Metastatic tumour most commonly occurs in the skeleton, lungs and liver (James *et al.*, 1972; Scott *et al.*, 1982; Shapiro *et al.*, 1984).

Localisation of phaeochromocytoma presents an interesting diagnostic challenge. Ultrasound is an excellent imaging procedure which identifies most large, bulky tumours, usually over 30 mm in diameter. Within these tumours there is usually a regular echo pattern with trans-sonic areas representing haemorrhage or central necrosis within the phaeochromocytoma, as in Case 3. Calcification in the margin of the phaeochromocytoma will give dense echoes at ultrasound and will also be identified on plain radiography, as in Case 1. Scintigraphy using the relatively new compound ^{131}I metaiodobenzyl guanidine (^{131}I-MIBG) has allowed more accurate localisation of both primary and metastatic disease (Shapiro *et al.*, 1984; Thompson *et al.*, 1984).

Computed tomography is highly accurate in identifying both mass lesions and the normal adrenal gland. Phaeochromocytomas are normally homogeneous, with reasonably well defined margins as in Case 4. Central necrosis and haemorrhage will produce low density areas within the centre and a fixed peripheral rim of tissue. Should CT not be available, ultrasound will identify most of these large tumours. When the findings at ultrasound and scintigraphy are inconclusive and review of the biochemistry indicates the likelihood of phaeochromocytoma, non-selective adrenal arteriography may prove to be a definitive investigation, particularly in vascular lesions, identifying both those within the adrenal and those situated extra-adrenally at the renal hilum or in the organ of Zuckerkandl. Occasionally these tumours may be avascular, as in the first patient. Arteriography carries a slight risk in that hypertensive episodes may be provoked and adrenergic blockade should be carried out. Should the arteriogram be negative and biochemistry still indicative of a phaeochromocytoma, it is likely to be extra-adrenal in situation. Catheterisation of the inferior vena cava with sampling of the venous plasma for catecholamines may then be required.

Using ultrasound, CT and arteriography it is not easy to be certain that one is dealing with a malignant phaeochromocytoma. Irregular invasive margins will certainly raise the possibility but these features are rarely seen. The presence of multiple metastases either on plain radiographs or on bone scintigraphy are highly suggestive of a malignant phaeochromocytoma.

The hormonal function of these tumours is variable, but the majority predominantly secrete noradrenalin, and patients usually exhibit symptoms of excess catecholamine secretion. Measurement of the serum noradrenalin or the urinary product normetadrenalin may be used as a tumour marker (Brennan and Keiser, 1982; Shapiro *et al.*, 1984). Persistence or recurrence of symptoms, together with elevated levels of catecholamines, may indicate either failure of primary surgical treatment or the presence of residual or functioning metastatic tumour (Brennan and Keiser, 1982).

Conventional treatment has been based upon surgical resection of the tumour and control of the symptoms of excess catecholamine secretion using both alpha and beta adrenergic blockade (Modlin *et al.*, 1979; Brennan and Keiser, 1982; Van Heerden *et al.*, 1982). Experience in the management of metastatic phaeochromocytoma with chemotherapy is limited and the results to date are not encouraging. Various combinations of antitumour agents have been used and limited success has been obtained with combinations of Adriamycin plus streptozotocin (Brennan and Keiser, 1982) and vincristine, BCNU and Adriamycin (Scott *et al.*, 1982). The successful use of streptozotocin in the treatment of neuroendocrine tumours of the gastrointestinal tract (Broder and Carter, 1973) suggested that it might be useful in the treatment of malignant phaeochromocytoma. Results, however, have been disappointing (Hamilton *et al.*, 1977; Scott *et al.*, 1982). More recently, ^{131}I-MIBG has been used and whilst early results are encouraging, long-term results are awaited (Shapiro *et al.*, 1984; Thompson *et al.*, 1984). Painful bony metastases respond well to radiotherapy (James *et al.*, 1972) and localised or solitary soft tissue metastases may be surgically resected.

Survival data relating to patients with malignant phaeochromocytoma are difficult to assess because of the rarity of the tumour. The largest series reported is from the Mayo Clinic (Remine *et al.*, 1974; Van Heerden *et al.*, 1982), in which 33 patients presenting between 1926 and 1980 were studied; the 5-year survival rate was 36%. The majority of patients who died from malignant phaeochromocytoma did so within 3 years of the appearance of metastases.

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The Authors

H. J. E. Lewi, FRCS, Senior Registrar in Urology.
R. Reid, MB, ChB, Senior Registrar in Pathology.
B. Mucci, MB, ChB, Registrar in Radiology.
J. K. Davidson, MD, FRCP, FRCR, Consultant Radiologist.
K. F. Kyle, FRCS, Consultant Urologist.
S. G. Macpherson, FRCS, Senior Lecturer in Surgery.
P. Semple, MD, FRCP, Consultant Physician.
S. Kaye, MD, MRCP, Senior Lecturer in Oncology.

Requests for reprints to: H. J. E. Lewi, Department of Urology, Western Infirmary, Glasgow G11 6NT.

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Selection of Operative Procedure for Circumcaval Ureter (Type I)

A Rational Approach

SANTOSH KUMAR and M. BHANDARI

Department of Urology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

Summary—The surgical treatment of circumcaval ureter (type I) should eliminate the ureteric obstruction which is of variable causation. At operation, the aetiology of the obstruction can be determined by inspection of the extent of ureteric dilatation, perfusion-pressure study and calibration of the lumen. Using this approach, the cause of the obstruction was found to be non-stenotic intrinsic obstruction of the retrocaval segment in two cases of type I circumcaval ureter. In these patients, resection of the obstructing segment and uretero-ureterostomy were carried out. The third patient had pelviureteric junction stenosis which was treated by dismembered pyeloplasty after ureteric relocation.

Circumcaval ureter has been classified into two types depending on the level of uretero-caval crossover (Kenawi and Williams, 1976). In type I the ureter crosses behind the inferior vena cava at the level of the third lumbar vertebra. In the less common type II the crossover occurs higher, at the level of the renal pelvis. Type I is associated with ureteric obstruction which may be either extrinsic (compression by the inferior vena cava, the psoas border or a lumbar vein; kinking) or intrinsic (stricture of the pelviureteric area or the retrocaval segment) (Kenawi and Williams, 1976). Operative correction has involved procedures either on the ureter, such as pelviureteric or uretero-ureteric anastomosis, with or without resection of the retrocaval segment, or, rarely, on the vena cava. We report three cases of type I circumcaval ureter in which selection of the operative procedure was based on the accurate definition of the nature of the obstruction by a combination of operative inspection of the extent of the ureteric dilatation, intra-operative pressure study and ureteric calibration.

Case Reports

Case 1 An IVU performed during investigation of a 32-year-old woman for urinary tract infection revealed right hydronephrosis and a dilated proximal ureter. Right retrograde pyelography confirmed a type I retrocaval ureter. At operation the dilated ureter was found to extend up to the edge of the vena cava (Fig. 1). Perfusion-pressure study was performed using a needle attached to a polythene tube which was connected through a Y-connection to a saline manometer and a saline container incorporating a drip chamber. The needle was inserted into the pelvis and saline was infused, starting at a rate of 1 ml/min and increasing gradually to 10 ml/min. A corresponding rise in the pelvic pressure above the basal level was recorded at different infusion rates. A pressure rise of 10 cm of saline or more above the basal level with an infusion rate of 10 ml/min was taken to denote a significant obstruction. In this case a pressure rise of 16 cm of saline was noted with an infusion rate of 10 ml/min. The retrocaval segment was marked with 4/0 silk sutures, mobilised and delivered to the right of the vena cava. Repeat pressure study showed a similar pressure rise, thus ruling out extrinsic obstruction in the retrocaval segment. This segment showed failure of peristaltic transmission. Through a pyelotomy, a 6F catheter could be easily passed down the ureter,

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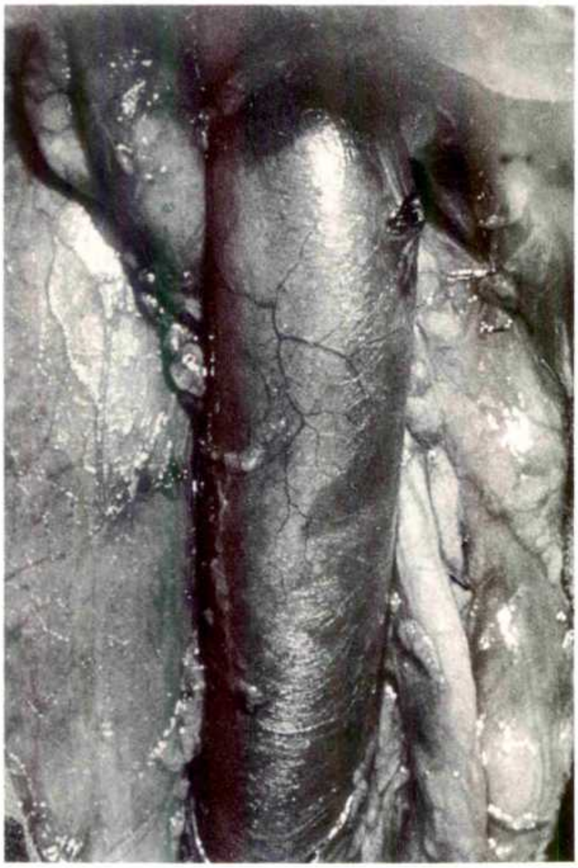

Fig. 1 (*Case 1*) Ureteric dilatation up to the edge of the vena cava.

ruling out intrinsic stenosis. With a diagnosis of non-stenotic obstruction of the retrocaval segment, the latter was resected. After ureteric relocation, a spatulated end-to-end ureteric anastomosis was performed. Histological examination of the retrocaval segment revealed fibrous replacement of the muscle layer (Fig.2). A follow-up IVU showed regression of the right hydronephrosis and satisfactory drainage of the kidney.

Case 2 An 18-year-old boy presented with a 1-year history of right flank pain. A plain abdominal film showed a stone in the right kidney. IVU demonstrated right hydronephrosis with dilatation of the upper third of the ureter. A prone film revealed a medially deviated middle portion of the ureter, confirming the diagnosis of circumcaval ureter. At operation the ureter was found to be dilated up to the caval edge (Fig. 3). A pressure study, performed as in case 1, showed a pressure rise of 19 cm of saline with an infusion rate of 10 ml/min. After marking, the retrocaval segment was released from behind the cava and brought to its right side. Repeat pressure study showed a similar pressure rise, confirming the absence of extrinsic obstruction. Transpyelotomy calibration of the ureter with a 6 F catheter showed the calibre of the retrocaval segment to be adequate. The single renal pelvic stone was removed. As in case 1, resection of the retrocaval segment and spatulated uretero-ureterostomy were performed. Histological examination of the retrocaval segment showed fibrous replacement of the muscular layer similar to that found in case 1. The post-operative IVU was satisfactory.

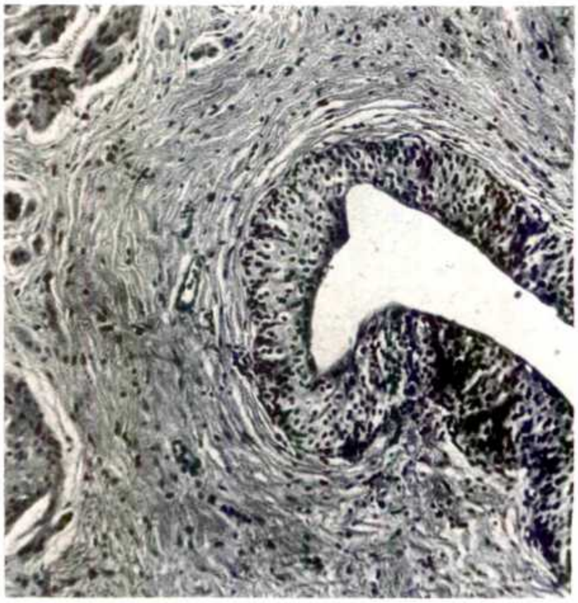

Fig. 2 (*Case 1*) Fibrous replacement of ureteric muscle in the retrocaval segment (H and E × 60).

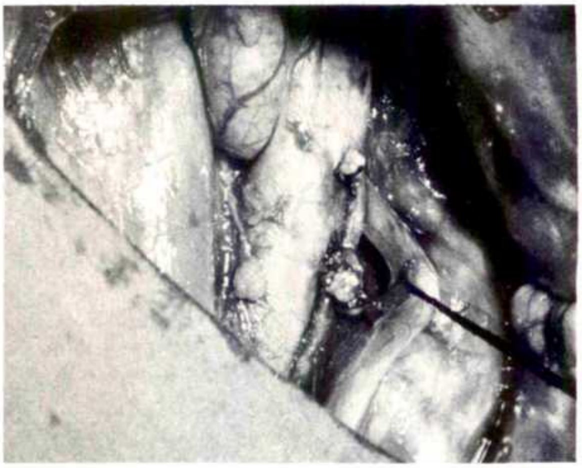

Fig. 3 (*Case 2*) Ureteric dilatation up to the vena cava. The distal ureter is held in a sling.

Case 3 A 25-year-old man presented with right flank pain of 2 years' duration. X-rays of the kidney, ureter and bladder showed a calculus in the right kidney. An IVU demonstrated dilated right renal calices and pelvis with non-visualisation of the ureter. At right renal exploration a type I circumcaval ureter was found. The renal pelvis was dilated but the ureteric segment between the pelviureteric junction and the vena cava was not dilated. The peristaltic wave did not appear to be transmitted across the pelviureteric area. Through a pyelotomy, attempted calibration of the pelviureteric junction with a 6 F catheter failed, confirming the stenosis. A pelvic stone was removed. The stenotic pelviureteric junction was resected, the ureter relocated, and a dismembered pyeloplasty performed. After 3 years' follow-up, the patient remains asymptomatic and the post-operative IVU is satisfactory.

Discussion

The nature of the ureteric obstruction in type I circumcaval ureter has been controversial and various extrinsic and intrinsic factors have been implicated. Logically, compression by the inferior vena cava cannot be the predominant cause of obstruction because type II circumcaval ureter is seldom associated with marked obstructive features. It has been found that ureteric dilatation generally stops short of the edge of the vena cava and hence extrinsic compression by a lumbar vein or the psoas border has been implicated (Bateson and Atkinson, 1969). An intrinsic anomaly of the retrocaval segment has also been described as the cause of obstruction (Carrion *et al.*, 1979; Reese and Hanna, 1980). Two of our patients had dilatation of the ureter up to the caval edge and non-stenotic obstruction of the retrocaval segment. In the third case the dilatation of the ureter stopped short of the vena cava and there was a pelviureteric stenosis.

Various types of operative procedure have been performed for the correction of type I circumcaval ureter. A few patients have had caval division, repositioning of the ureter and reanastomosis. However, with modern developments in the technique of ureteric anastomosis, caval procedures are seldom needed. Furthermore, caval surgery alone will not correct an intrinsic ureteric anomaly. Pelviureteric anastomosis and uretero-ureterostomy have been the reconstructive procedures most often performed for type I circumcaval ureter (Kenawi and Williams, 1976). In some cases they have been combined with resection of the retrocaval segment. There is no single operative procedure applicable to all cases of type I circumcaval ureter because of differing obstructive lesions. We recommend our approach of operative inspection of the extent of the dilated ureter (up to the vena caval margin or stopping short of it), intra-operative pressure studies (before and after mobilisation and delivery of the retrocaval segment to the right of the inferior vena cava to differentiate between extrinsic and intrinsic obstruction), and ureteric calibration (to classify intrinsic obstruction into stenotic and non-stenotic types). These tests will diagnose the cause of obstruction and guide the choice of the appropriate surgical procedure in the individual case.

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The Authors

Santosh Kumar, MS, MCh, Associate Professor of Urology.
M. Bhandari, MS, MCh, Professor and Head of Department of Urology.

Requests for reprints to: M. Bhandari, Department of Urology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India 605 006.

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A Simple Loop Catheter for Ureteric Calculus Retrieval

S. V. KOTWAL, G. S. KOCHHAR, N. P. GUPTA and S. M. SINGH

Department of Urology, All India Institute of Medical Sciences, New Delhi, India

Summary—The fabrication and use of a simple looped catheter for ureteric stone retrieval are reported. In a series of 46 patients the loop was passed successfully in 28 and the stone dislodged in 20 (71.4%). This device can be made by any urologist, using cheap, readily available materials. Complications are few and the success rate is high.

Ureteric calculi occupy much of the urologist's time and attention and non-operative methods have much to commend them. While basket extractors are widely used in the lower 5 cm of the ureter, the loop catheter can be used for calculi (even large and multiple ones) anywhere in the ureter, whether infection is present or not (Tsuang and Evans, 1983). The patented loop catheters popular in the United States and Europe cost about Rs. 350.00 each in India and are not readily available. We have therefore devised a simple loop catheter which costs about Rs. 30.00 and report our experience of its use in 46 patients.

Patients and Methods

Preparation of the looped catheter

After trying out various makes, we found the Porges plastic round-tip ureteric catheter ideal for making the looped catheter. We frequently used the 6 F size and a 3/0 needled nylon suture (76 cm) for preparing the device. For larger stones we used the 7 F catheter and in one patient with a grossly dilated ureter with multiple calculi we even used an 8 F catheter.

To make the looped catheter, the needle of the nylon suture is held with a needle holder. It is then passed through the subterminal hole of a catheter and brought out through the centre of the solid tip. A terminal knot is tied at the end of the nylon suture and the suture drawn out so that the small knot fits snugly in the lumen of the tip of the catheter. The needle is then cut off. A small side-hole is made at a predetermined length from the tip of the catheter with sharp scissors or a small knife. We made this hole 6 cm from the tip for a 6 F catheter and 7 cm from the tip for a 7 F catheter. The cut end of the nylon suture is then fed carefully through this side-hole so as to emerge at the butt-end of the catheter. The end of the suture when drawn upon causes the tip to curve upon itself to form a loop (Fig. 1). The prepared loop catheter is sterilised in Cidex and is used only once (Evans, 1979).

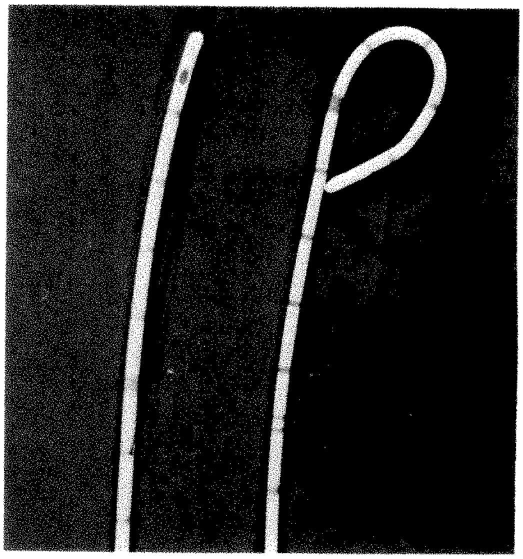

Fig. 1 Loop catheter, open and closed.

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Case selection. We did not adhere to the rigid criteria of patient selection recommended by Ipiens-Aznar (1982) and our indications for selecting a patient for a trial of loop retrieval were as follows:

(i) Calculi over 5 mm in length in the lower third of the ureter.
(ii) Upper and mid-ureteric calculi.
(iii) Multiple ureteric calculi.
(iv) Failed Dormia basketing.
(v) Calculus anuria.
(vi) Calculi with infection.

Thirty-seven male and nine female patients underwent a trial of loop retrieval between February 1983 and June 1984. The youngest patient was 14 years old and the oldest 55.

Twenty-four patients had right ureteric calculi and 23 had calculi in the left ureter. One patient had bilateral ureteric calculi treated simultaneously and nine patients had more than one stone. Three patients with solitary kidneys presented with calculus anuria.

The calculi were in the upper third of the ureter in 2 patients, in the middle third in 13 and in the lower third in 34.

Four patients presented with severe urinary tract infection and were given pre-operative antibiotic cover.

Pre-operative evaluation

Routine haematological and biochemical measurements were estimated in all cases. Urine culture and intravenous urography were mandatory. An X-ray was routinely performed on the endoscopy table immediately before starting the procedure.

Manipulative technique

General anaesthesia was used in 24 patients, spinal anaesthesia in 18 and local in 4.

We used a standard 19 F Storz cystoscope for all patients but one who required an 8 F loop catheter and a 23.5 F cystoscope. A wire stylet was used while inserting the loop catheter beyond the calculus. Bypassing the calculus was often easy but inability to do so was the major cause of failure in 18 patients. A determined effort was made to bypass the stone and we found the method described by Evans (1979) (repeatedly withdrawing and propelling the catheter) useful in difficult cases. A bulb-tip catheter, the Blassucci spiral-tip catheter or a smaller ureteric catheter were all occasionally helpful. We encountered no complications as a result of these manipulations.

Once the calculus was bypassed, we advanced the loop catheter with its stylet up to the 25 cm mark and then withdrew the stylet. The catheter was then gently advanced into the renal pelvis until mild resistance was felt or an X-ray confirmed its position (confirmatory X-ray was done only in our early cases). At this stage the loop was formed in the pelvis by holding on to the tip of the nylon suture and advancing the catheter over it. In the early days of the trial we usually took an X-ray at this stage to confirm that the loop had fully turned, but with increasing experience and confidence we could judge that the loop had formed by our inability to draw the nylon suture further and an additional X-ray was judged unnecessary. After the loop was formed we withdrew the loop catheter below the pelviureteric junction into the upper ureter, when further traction on the nylon suture was unnecessary as the ureteric walls gripped the loop and prevented it from uncurling. Depending upon the location of the calculus, the catheter was withdrawn so as to leave the loop lying above the calculus and this position was confirmed by X-ray. (This was the only X-ray film exposed intra-operatively in most of our cases). The cystoscope was carefully withdrawn without pulling the loop catheter any further. An appropriately sized hypodermic needle was fitted into the butt-end of the catheter and connected to a urine bag.

Post-operative management

Our first few patients were hospitalised until loop and calculus were delivered. Owing to pressure on hospital beds, however, we treated 38 patients as out-patients after detaining them overnight. Patients with calculus anuria, those with significant urinary infection and those who required further surgery for concurrent renal calculi, *etc*, were managed as in-patients.

We employed prophylactic chemotherapy with sulphamethoxazole—trimethoprim for all patients except those who had positive pre-operative urine cultures and they were given appropriate antibiotics.

All except seven patients were free of significant pain, could void freely alongside the catheter and were fully ambulant. They had no difficulty in observing post-operative instructions to drink plenty of fluids, to wear wrap-around clothing, not trousers or pyjamas, so that the loop catheter could hang freely from the external meatus at all times and not get pulled upon, and to walk about as much as possible so that loop progression was aided by gravity.

X-rays were done post-operatively on alternate days to check the position of loop and calculus.

Out-patients were also reviewed on alternate days to look for complications and to ensure that our instructions were being followed. We did not employ traction on the catheter at any stage, preferring to rely on spontaneous peristalsis, because our first few patients reported urethral pain even when a small weight was attached to the catheter. A confirmatory X-ray was done in all cases after the loop and calculus were voided.

Results

Forty-six patients took part in the trial between Feburary 1983 and June 1984.

Thirty-six patients required only one attempt at dislodging the stone and a second attempt was made in only 10 failed cases. Inability to bypass the stone with the catheter was the main cause of failure and we encountered this mainly in large, impacted or long-standing calculi with hydroureteronephrosis.

The overall results are given in the Table.

Table Overall Results

Total number of patients	46
Loop successfully formed	28
Failure to bypass	18
Successful retrieval	20
Number of procedures	56

The successful retrieval rate with a well formed loop was 71.4% and overall successful results were 43.5%. The average time taken to void a well formed loop was 4.4 days. The stone was usually expelled with the loop or immediately afterwards.

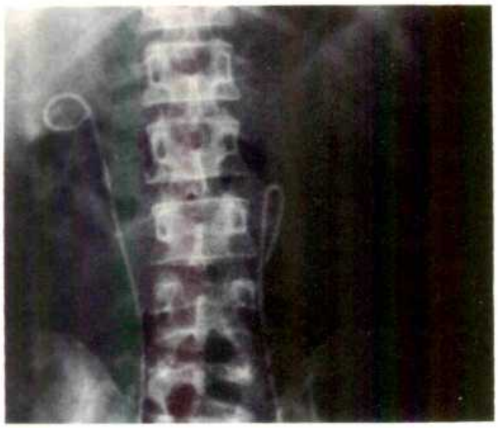

Fig. 2 Bilateral ureteric calculi retrieved successfully with bilateral loop insertion.

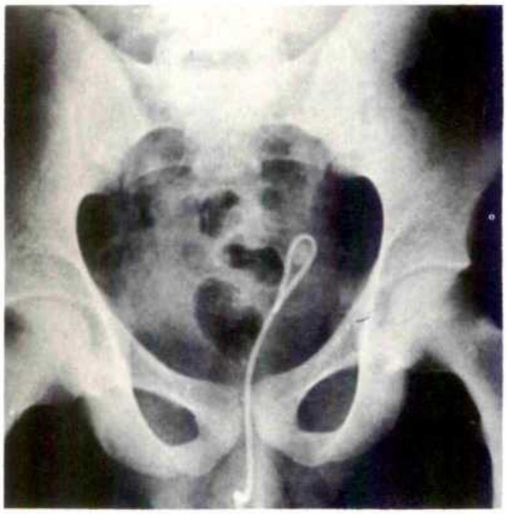

Fig. 3. Large ureteric calculus successfully retrieved.

Results in calculus anuria and unilateral renal agenesis were gratifying. Figure 2 shows a case of bilateral ureteric calculi for which two loop catheters were inserted simultaneously with successful results. The largest stone retrieved in this series was 1.3 cm in its longest axis (Fig. 3).

Failure to bypass the stone was the biggest problem, perhaps because we attempted this procedure for calculi of all sizes and location, whether impacted or not. At least two patients passed their calculi within 10 days of the failed procedure but cannot be counted as successful retrievals.

The complications encountered included urethral pain requiring analgesics in 7 patients, fever over 100°F in 2, post-operative infection in 4 and malformed loop in 3.

Discussion

The slow delivery method of calculus retrieval is attractive because of its safety and versatility in dislodging single or multiple stones anywhere in the ureter (Tsuang and Evans, 1983). Within limits, the size of the calculus is not a constraint (Evans, 1979). The stone basket is basically an extractor and serious complications have been reported with its use (Walsh, 1974; Blandy, 1978; Drach, 1978. The loop catheter, on the other hand, is not an extractor but acts as a skid which dilates the ureter and allows ureteric peristalsis to propel the smooth loop and entrapped calculus down the ureter (Evans, 1979).

Various types of loop catheter have been used. Zeiss introduced his device in 1939 and although this instrument is infrequently reported in the English literature, it remains quite popular on the Continent (Ipiens-Aznar, 1982). The Balkus (1943) loop had a short-lived popularity. The Ellik loop required intermittent traction and Ellik and Newton (1951) reported four ureteric ruptures, one nephrectomy and one death in a series of 74 patients. Evans (1979) reported a large series using his patented device with high retrieval rates and low complications. Tsuang and Evans (1983), in a very large series encompassing a 10-year experience, compared the results of ureterolithotomy, basket extraction and loop retrieval. While the retrieval rate was 46% for the loop and 71% for the basket, the authors were at pains to explain that the loop was used for higher and larger calculi (average diameter 6.9 mm) than the basket (average diameter 4.2 mm) and could be used for infected and multiple stones as well. It thus appears that the loop catheter merits a trial in a patient who would otherwise qualify for ureterolithotomy.

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The Authors

S. V. Kotwal, MS, MCh(Urol), Senior Resident.
G. S. Kochhar, MS, MCh(Urol), Senior Resident.
N. P. Gupta, MS, MCh(Urol), Assistant Professor.
S. M. Singh, FRCS, FAMS, Professor and Head, Department of Urology.

Requests for reprints to: S. V. Kotwal, 148 Base Hospital, c/o 56 APO, India.

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Unilateral Ureteric Reimplantation for Primary Vesicoureteric Reflux in Children

A Policy Re-evaluated

D. QUINLAN and BARRY O'DONNELL

Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Irish Republic

Summary—Fifty-one children had unilateral ureteric reimplants for primary vesicoureteric reflux over an 11-year period. Reflux was abolished in 50 patients but in 8 (15.7%) it developed or became worse on the contralateral side. An isotope renal scan (^{99m}Tc DMSA) was carried out in 15 of the 18 patients who had grossly scarred or dysplastic kidneys. Thirteen of these had less than 22% of total function coming from the affected kidney and seven had less than 10% of their total GFR coming from the kidney whose ureter had previously been reimplanted. Five of these children have undergone nephrectomy and it is felt that this would have been a better initial procedure. No patient was hypertensive at the conclusion of the study.

The precise pathogenesis of vesicoureteric reflux is still debated and perhaps because of this, antireflux surgery has remained a controversial subject. In the early sixties, when antireflux operations were first performed in large numbers, surgery was almost always bilateral because most affected children were thought to have associated bladder neck obstruction (Kelalis and King, 1976). Hutch (1961) and Tanagho *et al.* (1965) put forward the theory that a trigonal defect was responsible and this was also thought to be bilateral. Because both of these concepts had bilateral effects, bilateral surgery was advocated. A subsequent argument for bilateral reimplantation was the discovery that surgery on one side might cause reflux on the other (Warren *et al.*, 1972). Many surgeons now reimplant the contralateral side if there is or if there has been any degree of reflux, but some routinely reimplant the contralateral side regardless of the presence or absence of reflux. Spontaneous cure in lesser grades of vesicoureteric reflux is high (Lenaghan *et al.*, 1976) and therefore merits a conservative approach (Edwards *et al.*, 1977). In this hospital there are two surgeons (E. J. Guiney and B. O'Donnell) whose policy is to reimplant only those ureters with reflux grade 3, 4 or 5 (graded out of 5). Not all ureters with these grades are reimplanted, however. The contralateral ureter is treated entirely on its radiographic merits and reimplantation is undertaken only if it too demonstrates reflux grade 3, 4 or 5.

Patients and Methods

This series comprised 51 patients who underwent unilateral reimplant surgery for primary vesicoureteric reflux over the 11-year period 1972 to 1982 inclusive. Patients with duplex intravesical ureters, vesicoureteric obstruction, urethral valves or neurogenic bladders were excluded from the study, as were five patients with solitary kidneys. All patients were studied retrospectively. Results of pre- and post-operative micturating cystourethrograms (MCU), intravenous urograms (IVU), isotope renal scans, urine cultures and blood pressure measurements were evaluated. The result of the operation was studied in terms of reflux on the affected side, the effect of the operation on the

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opposite side, control of infection after surgery, and the effects of kidney growth, scarring and function. We also noted whether any patients were or became hypertensive during follow-up.

The patients' ages at operation ranged from 6 months to 11 years (mean 6 years). The 40 females (78%) in the series outnumbered the 11 males (22%) by almost 4 to 1, with males on average undergoing surgery 1 year earlier than females. The mean age at operation was 5 years for males and 6.3 for females. Operations were required on right-sided systems in 24 patients (47%) and on left-sided systems in 27 (53%). On average, patients were managed for 2.8 years pre-operatively from the time of their presentation with proven reflux. The duration of conservative management varied from 1 week to 7 years. The mean post-operative follow-up was 3.4 years.

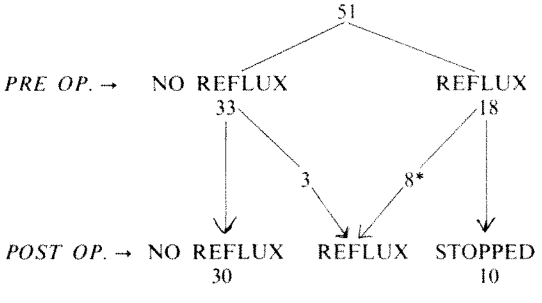
Of the 51 patients in the study 28 had their ureters reimplanted by the Leadbetter-Politano technique and 23 by the Cohen technique.

All patients had pre-operative MCUs: 14 patients had grade 5, 24 had grade 4 and 13 had grade 3 reflux. The mean pre-operative MCU score ipsilaterally was 4.02 out of 5.

Results

Reflux. Post-operative MCUs were available for all patients. Reflux was abolished completely in 50 patients and in 1 it improved from grade 3 to grade 1.

On the contralateral side, 33 patients had no reflux pre-operatively but post-operatively 2 patients developed grade 3 reflux and 1 had grade 4) (Fig. 1). Eighteen patients did have contralateral reflux pre-operatively and this disappeared in 10, improved in 1, remained static in 2 and deteriorated in 5. Of the patients in whom the reflux deteriorated on the contralateral side, two deteriorated from grade 2 to 4, one from grade 3 to 4, one from grade 2 to 3 and one from grade 1 to 4. Thus reflux on the opposite side developed or became worse in 8 of 51 patients (15.7%). Of these eight patients, one had a Cohen type reimplant and in the other seven the Leadbetter-Politano technique was used. Two of these patients subsequently required an antireflux procedure on the contralateral side.



* 5 worse, 2 same, 1 less.

Fig. 1 Outcome in 51 contralateral ureters.

Infection All patients had well documented pre- and post-operative serial urine cultures. Thirty-seven had infected urine pre-operatively and 14 had sterile urine. Of the 37 patients with infected urine pre-operatively 28 (75.7%) became sterile post-operatively. Of the nine patients whose urine remained infected post-operatively seven were female. One further patient whose urine was sterile pre-operatively developed urinary infections post-operatively.

Kidney growth and function All patients had pre- and post-operative intravenous urograms. Most had at least two annual IVUs post-operatively. Isotope renal scans were unavailable to us before 1980. Since that time, 19 patients have had the investigation (^{99m}Tc DMSA). Prior to 1980, IVUs with blood chemistry were used in the assessment of renal function. When pre- and post-operative IVUs were compared, the picture on the ipsilateral side seemed to have improved in 9, was unaltered in 22 and had deteriorated in 2. A further 18 patients showed ipsilateral kidneys that were grossly scarred or dysplastic from the start and these demonstrated poor growth and excretion both pre- and post-operatively. Fifteen of these 18 patients subsequently had isotope renal scans which showed that in 13 cases less than 22% of total function was coming from the affected kidney. Two showed a 27% and a 33% glomerular filtration rate contribution from the diseased kidney. Of the other four patients who had renal scans and whose IVUs looked reasonably good, none was shown to have less than 35% of function coming from one kidney.

Of the 13 patients who had less than 22% of their total GFR coming from the affected kidney, 7 had less than 10% coming from the kidney whose ureter had previously been reimplanted. Five of these patients have subsequently undergone nephrectomy. Nephrectomy was undertaken because it was not felt justified to leave *in situ* a grossly scarred kidney which was contributing less than 10% of total GFR. At operation grossly scarred

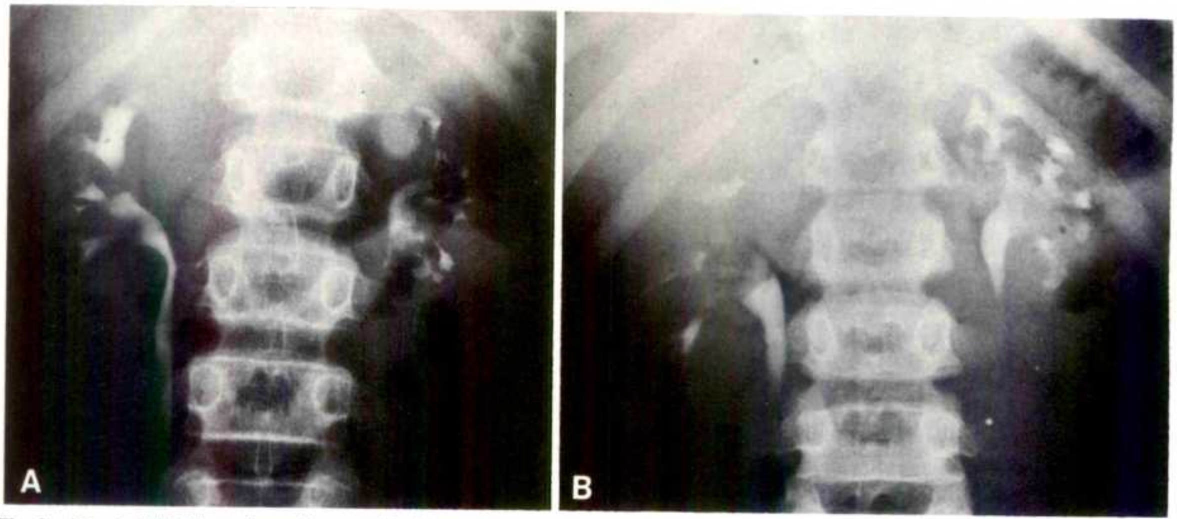


Fig. 2 15-min IVU films of two 11-year-old girls 5 years after antireflux ureteric reimplantation. (A) Left kidney contributed 11% of total GFR on isotope scan. Kidney weighed 20 g at nephrectomy. (B) Left kidney contributed 6% of total GFR on isotope scan. Kidney weighed 34 g at nephrectomy. Expected kidney weights: 110-130 g.

and shrunken kidneys were found. At the time of operation the expected weight of a normal kidney was between 110 and 130 g and the kidney specimens from these five nephrectomies weighed between 10 and 34 g (Fig. 2). A sixth patient is now booked for a nephrectomy and one has refused the operation.

On the contralateral side the IVU pictures were unaltered in 45 post-operatively and 6 other kidneys showed either improvement or compensatory hypertrophy.

Blood pressure No patient was found to be hypertensive during follow-up (Task Force on Blood Pressure Control in Children, 1977).

Discussion

This study was undertaken to determine the usefulness of unilateral reimplant surgery in controlling ureteric reflux, eradicating infection and sustaining or improving renal growth and function post-operatively.

In comparison with a large series by Willscher *et al.* (1976) of 223 patients with an average age of 3.4 years, our patients were older at operation (6 years) and our approach to reimplantation appears more conservative. The previously noted female to male preponderance is confirmed.

The effectiveness of reimplantation in eradicating reflux is shown. In only one patient did reflux persist and in this case there was a considerable improvement.

The hazard to the opposite side can be seen where 8 of 51 patients (15.7%) developed some degree of reflux (grade 3) or their pre-operative reflux became worse (grade 5). Two of these patients required a further operation. On our pre-operative criteria one could argue that all eight patients should have had revision contralateral surgery. The fact that post-operative MCUs showed a deterioration in contralateral reflux in five patients ran contrary to our general experience of the milder grades of reflux, where the condition tends eventually to disappear. Twenty-eight patients (75.7%) with infected urine pre-operatively had sterile urine post-operatively. These figures are similar to others quoted in the literature (Willscher *et al.*, 1976) and demonstrate the effectiveness of the operation in controlling infection.

In 18 patients where the refluxing ureter was reimplanted, the IVU showed the kidney on that side to be grossly scarred and to have poor function and growth. Of these 18, 15 had renal scans (^{99m}Tc DMSA) post-operatively and all showed a marked reduction in excretion on the affected side. Of the other patients who had renal scans but whose kidneys looked satisfactory on IVU, none had less than 35% of function in the affected kidney. IVU, though not a good guide to renal function, is useful in determining those shrunken and scarred kidneys which would merit renal scans.

Five patients (9.8%) have subsequently undergone nephrectomy for a kidney whose ureter was previously successfully reimplanted for reflux. We believe it inadvisable to leave such a diseased kidney *in situ* and risk the development of hypertension and further urinary tract infections. We advocate nephrectomy rather than ureteric reimplantation in any patient whose renal function from one side is less than 10% of the total. Because we did not have renal scanning until 1980 these five patients all had their renal scans post-operatively. Any patient who has significant scarring on IVU should have a renal scan before ureteric reimplantation. One patient is awaiting nephrectomy at the time of writing and a seventh patient has turned down this option. It would be speculative to say to what extent, if any, the reimplant helped these severely scarred kidneys to grow.

Some of the reasons for preferring nephrectomy to reimplantation and conservation of the kidney under these circumstances are:

(i) The affected kidney could not support life in the remote event of contralateral nephrectomy.
(ii) The necessity for a regular follow-up at least yearly throughout the life of any patient with a small scarred kidney. This would involve an ultrasound examination and possibly a renal scan, certain midstream urines for possible infection and a blood pressure estimation.
(iii) The condition would need to be stated on any medical certificate required for employment, pension or life insurance: so would nephrectomy, but the overtones are different.
(iv) The nature of the problems would need to be explained to potential spouses.
(v) The scarred kidney might cause problems during pregnancy.
(vi) The patient would continue to be a "patient" throughout his/her life.

Where a nephrectomy has been carried out and the urine is sterile our patients have been discharged from follow-up.

The unilateral reimplant appears justified and effective in dealing with selected cases. Following surgery, 3 of 33 patients (9.1%) developed reflux in a previously normal tract. All three would, on our criteria, require contralateral antireflux surgery. This is a distressing complication but it is not enough for us to advise prophylactic reimplantation of a non-refluxing system.

Of 18 patients who had unilateral reimplantation and "mild" reflux on the opposite side, reflux disappeared in 10, was unchanged in 3 and deteriorated in 5 (28%). If we stuck strictly to our criteria, these five would require a second reimplant operation. This probably represents an unacceptable figure and we now advise bilateral antireflux surgery where there is bilateral reflux with one side grade 3 or more.

Acknowledgements

Professor E. J. Guiney's patients have been included in this survey. We are grateful for his permission and assistance. The Radiological Department of Our Lady's Hospital for Sick Children carried out the radiological investigations and we acknowledge their assistance. We particularly wish to acknowledge the help of Dr G. J. Duffy, Physician in Charge, Nuclear Medicine Department, St Vincent's Hospital, Dublin, in whose department the isotope scans were carried out.

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The Authors

D. Quinlan, MB, FRCSI, Senior House Officer.
Barry O'Donnell, MCh, FRCS, FRCSI, Consultant Paediatric Surgeon.

Requests for reprints to: Barry O'Donnell, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Irish Republic.

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Ultrasound Assessment of Residual Urine

A Quantitative Method

C. J. M. BEACOCK, E. E. ROBERTS, R. W. M. REES and A. C. BUCK

Department of Urology, University Hospital of Wales, Cardiff

Summary—A method of measuring residual urine volume using ultrasound is described. The volume is computed from serial parallel sections of the bladder. This method is found to be significantly more accurate than previously reported techniques and is quick and easy to perform.

The assessment of residual urine forms an essential part of the investigation of many urological patients, particularly those with suspected urinary outflow obstruction; the presence of residual urine may influence their management. Whilst a qualitative demonstration of the presence of residual urine is readily obtainable from an intravenous urogram, a truly quantitative measurement has hitherto only been possible by catheterisation, but this carries risks of urinary infection and trauma to the urethra. Clearly a non-invasive method of measuring residual urine is desirable. Many techniques have been described, but all have had limitations, particularly with regard to accuracy (Bretland, 1958; Axelrod, 1966; Ravichandran and Fellows, 1983). We describe an ultrasound method for the measurement of residual urine that is quick, easy to perform, accurate and causes no discomfort to the patient.

Patients and Methods

Fifteen male patients (aged 55-80 years) undergoing investigation for urinary outflow obstruction were studied. Some were studied on more than one occasion and 25 paired readings of volumes of residual urine were obtained.

Each patient was asked to drink water until the urge to pass urine became irresistible. He then voided to completion in a standard flow-meter. A 12 F catheter was immediately passed and spigotted, thus avoiding delay between scanning and subsequent catheter drainage of the bladder. With the patient supine, an assessment of residual urine was made using a Searle/Siemens Phosonic SM Grey Scale Ultrasound machine with a digital scan converter. A PDP 11 series microprocessor is also incorporated in the unit. The ultrasound transducer is located at the end of a jointed boom which allows movement of the transducer in one plane only. The boom arm can be moved by predetermined intervals to allow serial sections to be scanned.

The bladder is located by longitudinal scanning and a transverse section obtained at the lowest possible level. Using a joystick located on the control panel, a cursor line can be constructed around the periphery of the bladder outline on the screen and the machine computes the area enclosed. By performing serial transverse scans at 0.5 cm intervals and calculating the area of each, the machine, when set in the volumetric phase, computes the cumulative volume outlined and the total residual urine volume is measured (Fig. 1). Using a 3 MHz transducer, the residual urine volume was measured on 25 occasions and compared with the volume subsequently drained from the catheter. The procedure took, on average, 5 minutes.

Results

The results are shown in Figure 2. Volumes measured ranged from 0 to 500 ml. The difference

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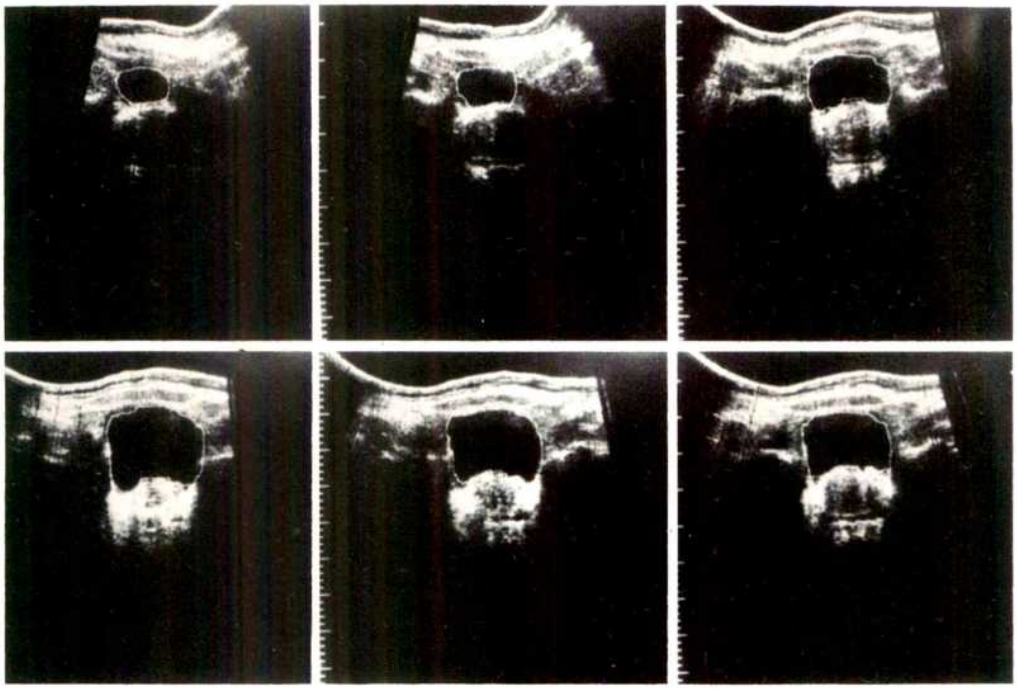

Fig. 1 Serial cross section scanning image of the bladder (anterior abdominal wall uppermost), with circumferential cursor line superimposed.

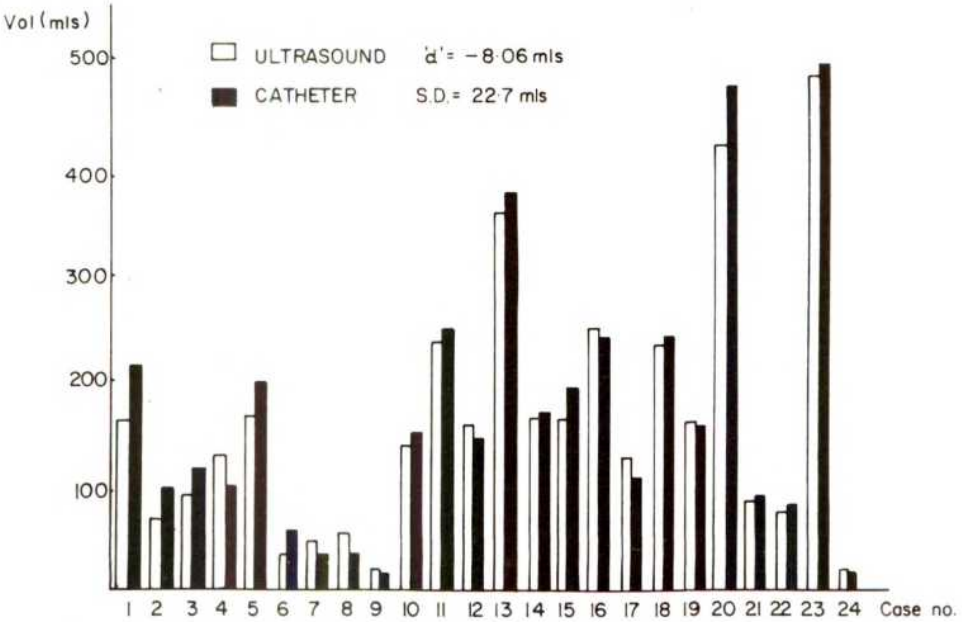

Fig. 2 Histogram showing the range of volumes of urine measured, illustrating the close agreement between the two methods.

between the two methods varied from 0 to 56 ml. A scatter diagram of ultrasound volumes versus catheter volumes was plotted (Fig. 3) and shows good correlation between the two methods (r = 0.994). The root mean square deviation was 24.12 ml, consisting of a bias of minus 8.6 ml in ultrasound urine as against catheter urine, and the standard deviation of the difference was 23.29 ml. A *t* test applied to the mean difference gave a non-significant result ($t = -1.67$).

Discussion

Previous studies have confirmed that ultrasound is a safe investigation for the measurement of residual urine. Many techniques have been described but the accuracy of the methods varies widely (Holmes, 1966; Pedersen *et al.*, 1975; Harrison *et al.*, 1976; Orgaz *et al.*, 1981). Usually one or more diameters of the bladder are measured and the volume is derived by the application of a complex formula (Holmes, 1966; Rageth and Langer, 1982). There is doubt, however, concerning the accuracy of mathematically derived empirical formulae for the estimation of residual urine, particularly if applied to a bladder or irregular shape as is often found in outflow obstruction; indeed, many workers comment that the most consistent results are obtained when examining normal or hypotonic bladders (Holmes, 1966; Orgaz *et al.*, 1981; Rageth and Langer, 1982). More recently the use of a hand-held or a portable ultrasound scanner for the assessment of residual urine has been described (Ravichandran and Fellows, 1983), but the inherent inaccuracy of a hand-held probe, with only half of the estimations being within 20% accurate and errors of up to 300%, outweighs the convenience of a bedside investigation; furthermore, these techniques give a qualitative rather than a quantitative measure.

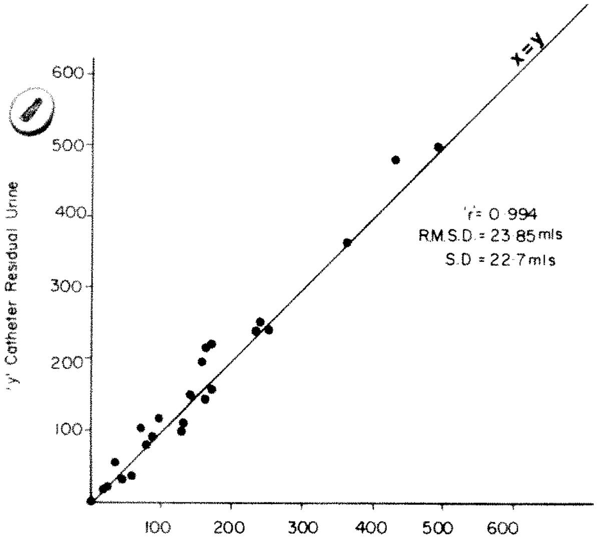

Fig. 3 Scatter diagram of ultrasound versus catheter residual urine volumes showing excellent correlation.

Volume computation by ultrasound scanning of serial parallel sections has been described for other organs, including the spleen and prostate (Dorst *et al.*, 1974; Brooman *et al.*, 1981; Hastak *et al.*, 1982). Although this technique has been considered unsuitable for bladder volume determination (Pedersen *et al.*, 1975), we have found it to be more accurate and without the disadvantages of previously described ultrasound methods, accuracy being achieved by the use of a transducer scanning in one plane only at predetermined intervals. The figure obtained is a direct measurement of the volume of the bladder and does not make assumptions about the shape of the bladder, which is often asymmetrical. This simple non-invasive technique for measuring residual urine is superior to those previously described. This degree of accuracy may not be essential in routine clinical practice, but in situations where an exact measurement is required it is the method of choice. A "B" scanner as used in this method is still widely available in most hospitals in the UK and the technique can be readily adapted to the more modern real-time ultrasound scanners, many of which have suitable programmes for volume computation.

It is concluded that this new method for the assessment of residual urine offers all of the traditional benefits of ultrasound examination and is more accurate than previously described non-invasive techniques. Determination of residual urine is best performed by sonographic measurement and its volume computed from serial parallel sections of the bladder.

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We thank Professor K. Evans for permission to use the facilities of the Department of Radiology and Dr Newcombe, Lecturer in Medical Statistics, for help in the statistical analysis.

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The Authors

C. J. M. Beacock, FRCS, Lecturer in Urology.
E. E. Roberts, DCR, Research Radiographer.
R. W. M. Rees, FRCS, Consultant Urologist.
A. C. Buck, FRCS, Senior Lecturer in Urology.

Requests for reprints to: C. J. M. Beacock, Department of Urology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

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Low Pressure/Low Flow Voiding in Younger Men: Psychological Aspects

J. C. BARNES, G. HARRISON and K. MURRAY

Clinical Investigation Unit, Ham Green Hospital, Bristol

Summary—Low pressure/low flow voiding in young and middle-aged males in the absence of outflow tract obstruction has been reported as being associated with anxiety and a high incidence of dyspepsia. To assess objectively the psychological basis of this condition, an unselected group of 50 men aged 25 to 55 years was evaluated by psychiatric interview, questionnaires and urodynamic tests. In addition, patients involved in an earlier study were psychologically evaluated. Low pressure/low flow voiding was demonstrated in three (6%) of the new patients. This voiding pattern was related to a long preceding history, stress-dependent symptoms and difficulty in voiding in public urinals. When compared with a control population, the experimental group scored significantly higher on measures of psychoneurosis. It is recommended that surgery be avoided in these patients and that simple behavioural therapy may be most appropriate.

An ancient Chinese dictum states that "the bladder is the mirror of the soul". Certainly it is within the experience of most individuals that urinary symptoms, especially frequency, occur during periods of stress. Whether or not long-term stress can lead to urinary symptoms becoming so prolonged and severe that patients present with lower urinary tract obstruction is uncertain. It is, of course, well recognised that psychological disturbance can become manifest in other somatic disorders such as asthma, peptic ulcers and skin conditions.

Dunlop (1979) reported on psychiatric problems in patients attending urological out-patient clinics and showed that patients with lower urinary tract symptoms scored higher on the Hamilton rating scale for depression than patients with upper tract symptoms. Using a simple urodynamic technique, Straub *et al.* (1949) demonstrated that changes in bladder function may occur as the only evident somatic accompaniment of an emotional response. In women, psychological problems associated with detrusor instability and both urge and genuine stress urinary incontinence are well recognised (Frewen, 1978; Hafner *et al.*, 1977) also reported psychological disturbance in female patients with urinary symptoms but normal urodynamics. In 1979, George and Slade described a group of 16 young men presenting with frequency, hesitancy and a poor stream associated with a low pressure/low flow voiding pattern on urodynamic assessment and with no endoscopic abnormality. These men tended to suffer from dyspepsia and reported psychological problems, particularly anxiety. They noted marked hesitancy when attempting to initiate micturition in a public urinal in the presence of others. The authors coined the term "the anxious bladder" to describe this group of patients. Their findings suggested that a high proportion of young men attending for urodynamic evaluation fell within this group. However, the study was uncontrolled, the assessment of psychological disorder admittedly subjective and it was unclear how patients were sampled.

To investigate these findings further, we compared a group of young men showing the urodynamic pattern of low pressure/low flow voiding with control groups of patients with other urodynamic diagnoses and with a standard reference group from the normal population.

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Patients and Methods

Fifty-three consecutive men, aged 25 to 55 years, referred from urological clinics for urodynamic evaluation were included in the study. Three were subsequently excluded, two having long-standing neurological disorders (multiple sclerosis, traumatic paraplegia) and another with recurrent urinary infection following nephrectomy. The remaining 50 had persistent lower urinary tract symptoms of unknown aetiology.

To ensure, as far as possible, that judgements were made without prior knowledge of the urodynamic diagnosis, patients first underwent psychological evaluation (J.C.B., G.H.). A semi-structured interview covered major life events in the 6 months preceding the onset of symptoms, medical, psychiatric, sexual and family history. Patients were asked to make a subjective assessment of the relation of their urinary symptoms to stressful events. In view of George and Slade's findings in 1979, patients were asked whether they had ever suffered from upper abdominal pain treated with antacids or investigated by barium X-ray studies. They then completed two self-rating questionnaires. The Crown-Crisp Experiential Index (Crown and Crisp, 1979) provided scores for the psychoneurotic traits of free floating anxiety, depression, obsessionality, phobic anxiety, functional somatic complaints and hysteria. The Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975) gave a score for the personality dimensions of extroversion, neuroticism, psychoticism and included a lie scale reflecting an individual's tendency to "fake good".

Eleven of George and Slade's original 16 "anxious bladder" patients showing a low pressure/low flow voiding pattern were available for re-evaluation and the psychological assessment alone was performed on these.

Urodynamic testing was performed by one author (K.M.). This consisted of a 7-day frequency/volume chart, initial free flow rate, medium fill (60 ml/min) filling and voiding cystometry and perfusion urethral profilometry (where indicated).

Saline (ambient temperature) filling was performed through a 10F Harris urethral catheter and intravesical pressure measured with a 16 G epidural catheter passed alongside the filling catheter. Intra-rectal pressure was measured with a fluid-filled balloon catheter. Pressures were measured using Elema Schonander EMT 34 transducers and displayed on an Elema Schonander Mingograf 81 ink-jet recorder. Detrusor pressure was obtained by electronic subtraction. Perfusion pressure profilometry was performed using an 8 F Porges catheter perfused at 2 ml/min and mechanically withdrawn at 5 mm/s.

For the purposes of comparison the 11 patients of George and Slade (1979), conforming to their urodynamic criteria of low pressure/low flow voiding, were treated together with our own patients with the same voiding pattern and hitherto referred to as the "experimental group".

Statistical analysis was performed using Fisher's exact probability and two tailed "t" tests.

Results

The urodynamic diagnoses of the 50 patients are shown in Table 1. The functional obstruction group were individuals with evidence of detrusor-urethral dyssynergia on voiding cystometry, the site of urethral obstruction being unclassifiable with the techniques used.

Table 1 Urodynamic Diagnosis of 50 New Referrals

	No. of patients	%
Normal	13	26
Normal and after contraction	6	12
Functional obstruction	9	18
Mechanical obstruction	8	16
Unstable ± obstruction	9	18
Experimental	3	6
Neuropathic	2	4

For the purpose of comparison of symptoms and previous medical history, two control groups were used; firstly those patients with normal urodynamics and then those with mechanical bladder outflow obstruction. In comparing the questionnaire scores, two groups of normal male volunteers were also used as controls (Eysenck and Eysenck, 1975; Crisp *et al.*, 1978).

Table 2 shows a comparison of the previous history of the normal, mechanically obstructed and experimental groups of patients. Several trends were apparent but failed to reach statistical significance. The experimental group had a prolonged preceding history of urinary symptoms but experienced no greater degree of frequency or nocturia than the other groups. They showed no tendency to childhood enuresis. Symptoms of outflow obstruction, namely hesitancy and a poor urinary stream, were common to both the experimental and mecha-

Table 2 Comparison of Previous Urological and Medical History

	Normal (*n = 13*) (%)	*Mechanical obstruction* (*n = 8*) (%)	*Experimental* (*n = 14*) (%)
Urinary symptoms 10 years	5 (38)	3 (37)	7 (50)
Diurnal frequency*	8.2 ± 0.8	9.7 ± 0.8	9.3 ± 0.7
Nocturia*	0.7 ± 0.3	1.1 ± 0.5	0.9 ± 0.3
Hesitancy	3 (23)	7 (87)	10 (91)†
Childhood enuresis	4 (31)	2 (25)	1 (10)‡
Reduced urinary stream	3 (23)	5 (63)	10 (87)§
"Stress" labile symptoms	2 (15)	1 (12)	7 (50)
Psychotropic medication by GP	4 (31)	3 (37)	8 (57)
Psychiatric referral	2 (15)	1 (12)	2 (14)
Public voiding difficulty	2 (15)	2 (25)	14 (100)
Dyspepsia	4 (31)	1 (12)	5 (35)
Marital difficulties	2 (15)	2 (25)	1 (7)
Sexual difficulties	4 (31)	3 (37)	4 (28)

* mean ± SEM † n = 11 ‡ n = 10 § n = 12

nically obstructed groups. In comparison with an obstructed control group, patients in the experimental group were four times more likely to relate a deterioration in their symptoms to periods of stress in their lives. They also reported an increased tendency to have been prescribed psychotropic medication (excluding hypnotics) by their G.P. There was no evidence for an increased rate of psychiatric referral. All patients in the experimental group reported a history of difficulty in voiding when in public lavatories, usually going back to adolescence. When compared with both control groups this difference reached a high level of significance ($P<0.0001$). We found no clear association with a history of dyspepsia.

In comparing the questionnaire scores (Table 3) the experimental group scored significantly higher for anxiety, obsessionality, depression, phobic anxiety and somatic complaints than a standard male population ($P<0.05$). They had a significantly higher lie scale score ($P<0.01$). The mechanically obstructed group scored significantly higher for anxiety ($P<0.01$) but for none of the other variables. However, when comparing the experimental group with either a control group with mechanical obstruction or indeed with all of the other urodynamic diagnostic groups combined, we found that they differed significantly only on the measure of obsessionality ($P<0.01$).

Discussion

This study represents an objective assessment of younger men with unexplained urinary symptoms using both urodynamics and standardised psychological techniques. The psychological symptoms developing secondary to distressing physical symptoms are largely controlled for by the experimental design.

We have shown that in an unselected consecutive series of younger male patients referred for urodynamic assessment, 6% have a dysfunctional voiding pattern characterised by low pressure and low flow during voiding cystometry. This rate compares with the rate of 19% reported by George and Slade (1979). The difference between these rates is probably accounted for by George and Slade's selection of patients known to have been previously resistant to treatment.

A possible criticism of this study could be that 11 of the experimental subjects were assessed psycho-

Table 3 Comparison of Psychological Questionnaire Scores with Standard Male Population. (All scores—mean ± SEM)

	Standard male population	*Mechanical obstruction* (*n = 8*)	*Experimental* (*n = 14*)
Anxiety (n = 316)*	3.0 ± 0.2	5.9 ± 1.0 ($P<.01$)	6.1 ± 1.2 ($P<.05$)
Obsessionality (n = 298)*	6.5 ± 0.2	5.9 ± 0.7 (N.S.)	9.9 ± 0.8 ($P<.01$)
Depression (n = 315)*	2.6 ± 0.1	3.6 ± 0.7 (N.S.)	4.8 ± 1.0 ($P<.05$)
Phobic anxiety (n = 314)*	3.0 ± 0.1	3.1 ± 0.5 (N.S.)	4.4 ± 0.9 ($P<.05$)
Somatic (n = 310)*	4.0 ± 0.2	5.6 ± 1.2 (N.S.)	6.1 ± 0.8 ($P<.05$)
Hysteria (n = 310)*	3.3 ± 0.2	5.1 ± 1.7 (N.S.)	3.6 ± 0.8 (N.S.)
Psychoticism (n = 2312)**	3.8 ± 0.06	3.6 ± 1.5 (N.S.)	2.8 ± 0.6 (N.S.)
Extroversion (n = 2312)**	13.2 ± 0.09	13.2 ± 1.6 (N.S.)	11.1 ± 1.3 (N.S.)
Neuroticism (n = 2312)**	9.8 ± 0.1	9.4 ± 0.8 (N.S.)	11.9 ± 1.6 (N.S.)
Lie scale (n = 2312)**	6.8 ± 0.08	8.4 ± 1.9 (N.S.)	11.1 ± 1.0 ($P<.01$)

* Crisp *et al.* (1978). ** Eysenck and Eysenck (1975).

logically 5 years after the urodynamic diagnosis was made. However, all patients in this group continued to complain of at least mild urinary symptoms, principally of frequency and most often when under stress. Of these 11 men, six clearly related the original reason for referral to a worsening of their symptoms during what they regarded as an especially traumatic time in their lives. Moreover, personality traits are, in part, fairly stable characteristics and in view of the way these men regarded their lives as now being more settled, one might expect any change in their test scores to be towards the norm. Therefore we felt justified in combining this group with patients more recently identified as showing a low pressure/low flow voiding pattern.

This study shows how patients with a low pressure/low flow voiding pattern are significantly different from the normal male population on a range of sub-tests in the Crown-Crisp Index. That they do not differ on their Eysenck Personality Questionnaire scores is interesting and might be accounted for by their tendency to "fake good" as shown by a significantly higher lie score.

When our experimental group was compared with a mechanically obstructed control group or even a combined group of all five other urodynamic diagnoses, they differed on the measure of obsessionality alone in both cases ($P<0.01$). By obsessionality is meant an excessive meticulousness, dislike of change, over-conscientiousness and a need to control not only others but also oneself and one's emotions. When compared with other patients they do not report feeling more anxious but rather appear to experience urinary symptoms in response to stressful situations. It must be said that our "assessment" of "stress" was subjective and crude, but a personal experience of stress appeared to be one important precipitating factor. We would speculate that in these particular obsessional personality types, the need to control feelings and events may channel the manifestation of stress into urinary symptoms. A predisposing vulnerability to urinary hesitancy is suggested by the finding that all of the men with a low pressure/low flow voiding pattern had difficulty with micturition in public urinals, and moreover this difficulty had usually preceded their symptoms by many years. It is possible that a lifetime experience of difficulty in voiding in public may have acted as an initial focus for their symptoms.

We were unable to confirm George and Slade's (1979) finding of an increased incidence of dyspeptic symptoms.

Blaivas and Norlen (1983), in examining the results of treatment for low pressure/low flow states in young men, found that neither empirical pharmacological treatment nor transurethral surgery had any beneficial effect. However, their initial results suggested that behaviour modification could effect a significant improvement.

It is concluded that younger men with low pressure/low flow voiding, George and Slade's "anxious bladder", are psychologically unusual but in the direction of obsessionality rather than anxiety. There is evidence that they show a lifelong tendency to over-control the process of micturition and are thus vulnerable to lower tract urinary symptoms when under stress. It is recommended that surgery be avoided and that the behaviour modification programme proposed by Blaivas and Norlen (1983) warrants further investigation and evaluation in this group of patients.

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The Authors

J. C. Barnes, MRCPsych, Senior Registrar in Psychiatry, Barrow Hospital, Bristol.

G. Harrison, MRCPsych, Consultant Psychiatrist, Department of Psychiatry, University Hospital, Nottingham.

K. Murray, MA, FRCS, Research Registrar in Urology, Clinical Investigation Unit, Ham Green Hospital, Bristol.

Requests for reprints to: J. C. Barnes, Glenside Hospital, Blackberry Hill, Stapleton, Bristol BS16 1DD.

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Atropine Blockade of Nerve-mediated Stimulation of the Human Detrusor

R. B. KINDER and A. R. MUNDY

Departments of Surgery and Urology, Guy's Hospital, London

Summary—The effect of atropine on the isometric contractile response of isolated human detrusor muscle strips to electrical field stimulation has been studied. A 94.1% reduction in the response in the presence of tetrodotoxin demonstrated the neuronal nature of the stimulus. Atropine caused a 92.7% inhibition of the response. It was concluded that the nerve-mediated stimulus in human detrusor is cholinergic in nature and that "atropine resistance" does not occur in man.

In 1895 Langley and Anderson showed that stimulation of the sacral outflow in the dog produced a detrusor contraction which was only partly inhibited by atropine. Since that time there have been numerous publications concerning the anomalous nature of excitatory neurotransmission in the bladders of several mammals, although there has been little work on the human bladder. There is broad agreement that the post-ganglionic pathways responsible for detrusor contraction are at least in part cholinergic because they can be partially inhibited by atropine and because acetylcholine causes the detrusor muscle to contract by acting on muscarinic receptors (Chesher and Thorp, 1965).

However, a consistent feature in almost all mammalian bladders has been that a significant part of the contractile response to a nerve-mediated stimulus remains resistant to cholinergic blockade with atropine, regardless of the experimental method employed (Taira, 1972). Indeed a number of authors have reported total resistance of such a response to atropine blockade (Chesher and Thorp, 1965; Ambache and Aboo Zar, 1970), and there is currently no satisfactory explanation for this phenomenon.

By contrast, atropine causes a very significant inhibition of normal micturition in man (Brindley and Craggs, 1975) although, as in animals, *in vitro* experiments with isolated human detrusor strips have demonstrated only partial inhibition of neuronally stimulated contractions by atropine (Hindmarsh *et al.*, 1977; Cowan and Daniel, 1983). The degree of atropine resistance of the human bladder would therefore appear to be less than in animals such as the guinea pig and rat, although a more pronounced degree of resistance has been found in patients with prostatic obstruction and detrusor instability than in normal subjects (Sjögren *et al.*, 1982).

Because of the lack of information about the behaviour of the human detrusor and the problems of extrapolating from animal studies, we decided to investigate the effect of atropine on contractions produced by nerve-mediated stimuli in the isolated human detrusor muscle strip.

Materials and Methods

Samples were taken from the dome of the bladder of patients at open operation and were stored in Krebs' solution (composition in mM: NaCl 118; KCl 4.7; $MgSO_4,7H_2O$ 1.18; $NaHCO_3$ 25; KH_2PO_4 1.03; $CaCl_2$ 2.5; glucose 11.1) at 4°C for 1 to 24 h (mean 17.5 h). Detrusor muscle strips measuring approximately 5 mm in length and 1 mm in diameter were dissected from the sample and each strip was suspended in a 1 ml jacketed organ bath containing Krebs' solution at 37°C and bubbled with 95%O_2; 5%CO_2. Gradual stretch

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was applied to the strip to give an initial tension of 5 g, measured isometrically using a Grass FT03 force-displacement transducer and a Devices M4 chart recorder. At least 90 minutes' equilibration was allowed, during which time the baseline tension spontaneously fell to a level of 0.5-1.2 g. Field stimulation was accomplished by means of parallel platinum electrodes and a Grass S44 stimulator using supramaximal voltage (70 V) and a pulse width of 0.5 ms. The muscle was stimulated for 20 s at 4-min intervals using a range of frequencies from 0.5 to 20 Hz. Frequency-response curves were constructed and were subsequently repeated in the presence of added drugs. The nerve-mediated nature of the stimulus was tested by measuring the response in the presence of tetrodotoxin, which blocks the Na^+ dependent action potential that occurs in autonomic nerves, 3×10^{-7} M. It was assumed that after tetrodotoxin any residual response would be due to direct muscle stimulation rather than the result of a nerve-mediated stimulus. The bath fluid was changed and field stimulation repeated to demonstrate recovery of the preparation. The strip was then incubated in the presence of atropine which was added to the bath in 10 µl aliquots to give a range of bath concentrations from 10^{-8} to 10^{-6} M. Field stimulation was then repeated and the responses of the muscle strip recorded.

Twenty-three samples were tested from 13 patients, all of whom had normal detrusor function as assessed by video-urodynamic studies.

Results

Field stimulation caused a rapid rise in isometric tension of the muscle preparation which reached a maximum within 20 s and which returned to the baseline level after cessation of the stimulus. The threshold frequency for a contractile response was 0.5 Hz and the magnitude of the contraction was then frequency-dependent up to 20 Hz (Fig. 1). At frequencies greater than 20 Hz no further increase in magnitude was achieved. The mean reduction in response to all frequencies caused by tetrodotoxin 3×10^{-7} M was 94.1% (SD ± 8.7; range 73-100). Inhibition was greatest at lowest frequencies (100% at 0.5-1 Hz; 91% at 15-20 Hz). Full recovery of the muscle strip was noted after changing the bath fluid.

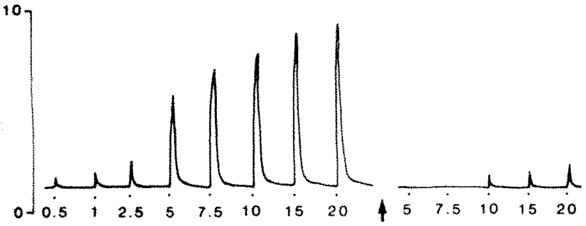

Fig. 1 Frequency-dependent responses of a human detrusor muscle strip to electrical field stimulation before and after the addition of atropine 10^{-7} M (arrow). Stimulation every 4 min at supramaximal voltage (70 V) and with a pulse width of 0.5 ms. Vertical scale shows change in isometric tension in grams.

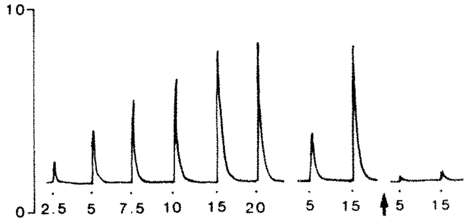

Fig. 2 Inhibition of the contractile response to field stimulation at 5 Hz and 15 Hz by atropine 10^{-7} M (arrow). Stimulation parameters as in Figure 1.

Atropine caused profound inhibition of the response to field stimulation within 10 to 12 min (Figs 1 and 2) and the degree of inhibition was dose-related. The mean maximum percentage reduction of the response by atropine 10^{-8} M in all samples tested and at all frequencies was 78.7% (SD ± 20.1; range 25-100%) and by atropine (10^{-7} M was 92.7% (SD ± 12.0 range 58-100%). Frequency-response curves before and after the addition of 10^{-7} M atropine are shown in Figure 3. Maximal inhibition was obtained with a bath concentration of 10^{-7} M atropine and increasing the dose to 10^{-6} M caused no further significant reduction in the response.

There was considerable variation in the inhibitory effect of atropine 10^{-8} M on samples from different bladders, while at a concentration of 10^{-7} M these differences became much less marked. As with tetrodotoxin, the magnitude of the residual resistant response was to some extent frequency-dependent, being more pronounced at the higher end of the range of frequencies used. However, although the percentage inhibition of the response to the higher frequencies was less than that at lower frequencies, the differences were not significant.

In those strips where there was apparent resistance to inhibition by atropine the residual contractile response to stimulation was only minimally affected by tetrodotoxin, which increased the degree of inhibition by less than 2%. Thus that part of the contractile response that was due to a nerve-mediated stimulus was largely abolished by atropine.

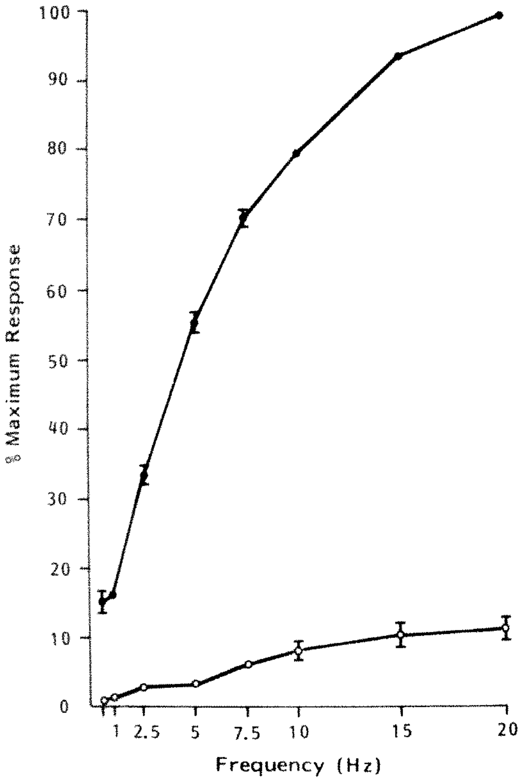

Fig. 3 Comparison of frequency-response curves before and after addition of atropine 10^{-7} M. Vertical bars represent standard error of the mean.

Discussion

The implication from animal studies that part or all of excitatory post-ganglionic neurotransmission in the bladder is resistant to atropine has led to a number of theoretical explanations. Carpenter (1977) argued that the apparent partial atropine resistance is a spurious finding related to an inaccessibility of "junctional" receptors to the drug which could nevertheless cause blockade at "extrajunctional" sites. An alternative theory is that acetylcholine is released in response to post-ganglionic stimulation in such high local concentrations as to prevent blockade by atropine (Huković *et al.*, 1965). This hypothesis has been discounted by Ambache and Aboo Zar (1970), who used much lower electrical stimulation parameters to avoid flooding the receptors with neurotransmitter, and by Dumsday (1971), who calculated that the "synaptic volume" was sufficient to allow access of atropine to the receptors.

This has stimulated the search for additional neurotransmitters in the mammalian bladder. The existence of an excitatory adrenergic pathway at this level has been excluded (Dean and Downie, 1978; Krell *et al.*, 1981), as have histamine and 5-hydroxytryptamine as neurotransmitters (Ambache and Aboo Zar, 1970). Adenosine triphosphate (ATP) causes contraction of detrusor muscle *in vitro* (Burnstock *et al.*, 1972) and is released during nerve-mediated stimulation of the guinea pig bladder (Burnstock *et al.*, 1978). The hypothesis that ATP is the non-cholinergic neurotransmitter has received some support (Andersson *et al.*, 1980), although the evidence in its favour has not been consistent (Weetman and Turner, 1977).

A contribution by prostaglandins to the ATP-induced contraction has been suggested (Andersson *et al.*, 1980), and in rabbit detrusor strips inhibition of prostaglandin synthesis reduced the response of the muscle to transmural electrical stimulation (Johns and Paton, 1976) and inhibited spontaneous activity (Bultitude *et al.*, 1976). In man, prostaglandins of the E and F groups cause contraction of detrusor strips (Abrams and Feneley, 1976; Andersson *et al.*, 1977), although the response tends to be slower and sustained for longer than those caused by ATP and acetylcholine.

Human detrusor muscle responds to pharmacological stimulation of muscarinic receptors by acetylcholine with a contraction which is totally blocked by atropine (Todd and Mack, 1969). Thus there seems little doubt that cholinergic pathways play a major part in excitatory neurotransmission in the bladder of man.

The present study has demonstrated almost total inhibition by atropine of the response to a nerve-mediated stimulus. A number of samples apparently exhibited "atropine resistance" in that a substantial part of the response (up to 42% in one strip) persisted in the presence of a maximally effective dose of atropine. However, the results showed a very similar comparative degree of inhibition of the response to field stimulation by atropine and tetrodotoxin. This suggests that the resistant component was almost totally due to direct muscle stimulation without the involvement of nerve pathways, with less than 2% of the maximum response over all frequencies being truly resistant to atropine blockade.

This study has revealed major differences in the degree of sensitivity of human detrusor muscle to cholinergic blockade when compared with previous animal studies. While it is possible that these are related to differences in the experimental model it seems more likely that in the human bladder, as distinct from some other mammals, excitatory neurotransmission is cholinergic in nature and that atropine resistance does not occur to any significant degree.

Acknowledgement

This study forms part of the work to be submitted as a thesis by R. B. Kinder for the MS Degree of the University of London.

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The Authors

R. B. Kinder, FRCS, Lecturer in Surgery.

A. R. Mundy, MS, FRCS, MRCP, Senior Lecturer and Consultant Urological Surgeon.

Requests for reprints to: R. B. Kinder, Department of Surgery, Guy's Hospital, St Thomas Street, London SE1 9RT.

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Perineal Nerve Damage in Genuine Stress Urinary Incontinence

An Electrophysiological Study

S. J. SNOOKS, D. F. BADENOCH, R. C. TIPTAFT and M. SWASH

The Sir Alan Parks Physiology Unit, St Mark's Hospital and Department of Urology, The London Hospital, London

Summary—Twelve patients with genuine stress incontinence of urine were investigated using manometric and electrophysiological techniques. All were shown to have slowed conduction in the perineal branch of the pudendal nerve which innervates the periurethral striated sphincter muscle. The mean perineal nerve terminal motor latency in these patients was 3.9 ± 0.8 (ms) and in 20 age and parity matched control subjects was 2.0 ± 0.2 (ms) ($P<0.001$). These results are consistent with a neurogenic factor in patients with genuine stress incontinence of urine which may have implications regarding selection of patients for surgery to restore urethral competence.

Slowed conduction in the distal segment of the pudendal nerve which innervates the external anal sphincter has been demonstrated in patients with idiopathic faecal incontinence (Kiff and Swash, 1984; Snooks *et al.*, 1985). Approximately 12% of patients with idiopathic faecal incontinence also have genuine urinary stress incontinence (Parks *et al.*, 1977). Slowed conduction in the branches of the pudendal nerves innervating the external anal sphincter and the periurethral striated sphincter muscles has been demonstrated in patients with double incontinence (Snooks and Swash, 1984a). In patients with faecal incontinence alone, however, the degree of slowed conduction in the perineal branch of the pudendal nerve that innervates the periurethral striated sphincter muscle is less marked than in those patients with both types of incontinence (Snooks *et al.*, 1984a).

Genuine stress incontinence of urine is defined as involuntary loss of urine when the intravesical pressure exceeds that of the maximal urethral pressure, in the absence of detrusor activity. Consequently the patient leaks urine when there is an elevation of intra-abdominal pressure. The urethral striated sphincter musculature comprises periurethral striated and intramural striated components, innervated by the perineal branch of the pudendal nerve and the pelvic efferent nerves respectively (Gosling, 1979). This dual innervation of the urethral striated sphincter musculature has also been demonstrated electrophysiologically (Snooks and Swash, 1984a).

In this report we present the results of proximal (cauda equina) and distal (pudendal nerve) motor conduction studies, together with other electrophysiological studies in patients with genuine stress incontinence of urine.

Patients

Twelve women aged 22 to 68 years (mean 47 years) were studied (Table 1). All had proven genuine stress incontinence of urine, each patient having undergone cystometrography. The duration of stress incontinence ranged from 0.5 to 11 years (mean 6 years). Ten patients were parous (mean parity 2, range 1-5). Two patients (cases 1 and 6) (Table 1) had experienced stress urinary incontinence since the delivery of their last child; both had undergone vaginal forceps deliveries. Eight patients had initially complained of urinary incontinence during pregnancy (Francis, 1960). Abdomi-

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Table 1 Clinical details

Patient No.	*Age (years)*	*Duration of incontinence (years)*	*Parity*	*Abdominal hysterectomy*
1*	22	0.5	1F	–
2	35	11	3	+
3	36	3	2	+
4	39	3	2	–
5	46	5	1	+
6*	50	11	5	–
7	50	4	3F	+
8	50	10	3	–
9	52	5	4	–
10	55	4	2	+
11	60	5	0	–
12	60	10	0	–

F = Forceps delivery.
* denotes urinary incontinence following childbirth (1) or last delivery (6).

Table 2 Physiology results

Physiological measurement	*Group I Incontinent of urine n = 12*	*Control subjects*	
Spinal latencies (ms)			
P1	5.0 ± 0.8	4.8 ± 0.4	n = 21
P4	3.6 ± 0.7	3.7 ± 0.5	
E1	5.8 ± 0.9	5.5 ± 0.4	
E4	4.6 ± 0.9	4.4 ± 0.4	
U1	5.6 ± 1.7	4.8 ± 0.3	n = 16
U4	4.5 ± 1.2	4.1 ± 0.3	
SLR	1.38 ± 0.11	1.30 ± 0.10	n = 21
Pudendal nerve terminal motor latency (ms)	2.0 ± 0.3	2.0 ± 0.2	n = 20
Perineal nerve terminal motor latency (ms)	3.9 ± 0.8*	2.4 ± 0.2	n = 20
Single fibre EMG fibre density (E)	1.62 ± 0.41	1.50 ± 0.19	n = 31
Manometry (cm of water) resting	46.4 ± 16.8	68.0 ± 11.9	n = 20
Voluntary contraction	82.5 ± 32.4	108.0 ± 45.8	

* Significant difference from controls ($P < 0.001$) (Wilcoxon Rank Sum Test).
P = puborectalis; E = external anal sphincter; U = urethral striated sphincter musculature.

nal hysterectomy had been performed on five patients for benign conditions. None of the 12 patients had evidence of either neurological or endocrinological disorder and no surgery had been performed on the bladder neck. There was no history of constipation and/or defaecation straining in these patients, factors which can lead to pudendal nerve damage (Kiff *et al.*, 1984). On examination, five patients had evidence of perineal descent, defined as ballooning of the perineum beneath the plane of the ischial tuberosities (Henry *et al.*, 1982). All 12 patients had clinically demonstrable anal reflexes.

Thirty-one age and parity matched patients attending St Mark's Hospital for the treatment of benign colonic polyps, all of whom had a normal defaecatory pattern with no evidence of neurological or endocrinological disorder, served as controls (Table 2).

Methods

Transcutaneous spinal stimulation

Transcutaneous spinal stimulation was achieved using the method devised by Merton *et al.* (1982). This technique was applied to assess the innervation of the urethral striated sphincter musculature (Snooks and Swash, 1984a and b) and the puborectalis and external anal sphincter muscles (Snooks *et al.*, 1985).

Digitally directed pudendal and perineal nerve terminal motor latency measurements

Both of these methods were developed from the technique of electroejaculation described by Brindley (1981) for use in patients with impotence due to paraplegia. The method for both pudendal and perineal nerve terminal motor latencies has been previously described elsewhere (Kiff and Swash, 1984; Snooks and Swash, 1984a and b).

Single fibre electromyography (EMG) of the external anal sphincter muscle

Single fibre EMG was used to measure the fibre density in the external anal sphincter muscle using the method developed in our laboratory (Neill and Swash, 1980). Single fibre EMG fibre densities in the incontinent patients were compared with normal values. The fibre density represents the mean number of muscle fibres recorded within the uptake area of the electrode in 20 different positions in the muscle (Stalberg and Trontelj, 1979; Neill *et al.*, 1981).

Anorectal manometry

The resulting tone and maximal voluntary contraction pressures in the anal sphincter zone were measured by manometry using standard techniques (Neill *et al.*, 1981).

Statistical methods

Non-parametric statistical significance testing was performed using the Wilcoxon Rank Sum Test.

Results

There was a significant increase in the perineal nerve terminal motor latency in the 12 patients with genuine stress incontinence of urine (Fig. 1) compared with the control subjects ($P<0.001$) but there were no differences between the patients' and control subjects' pudendal nerve terminal motor latency measurements.

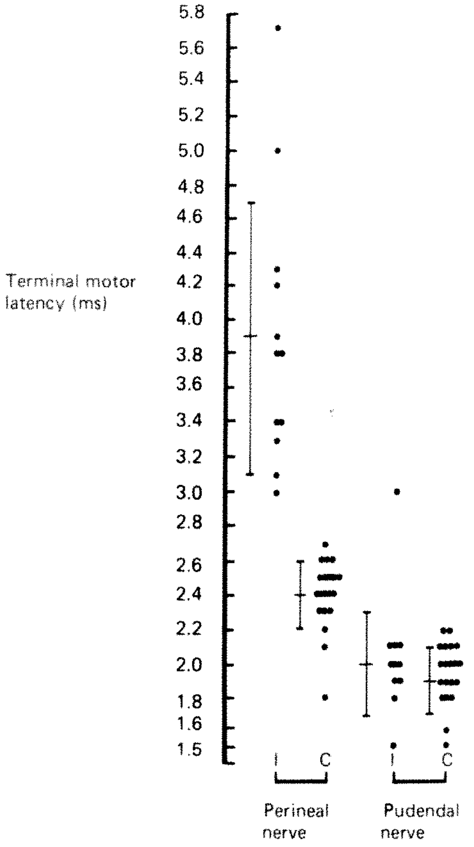

Fig. 1 Distribution of perineal and pudendal nerve terminal latencies in patients with urinary incontinence (I) and control subjects (C).

Proximal (cauda equina) conduction in these patients was normal and the spinal latency ratio was within normal limits (Snooks and Swash, 1985) (Table 2). Two patients (cases 3 and 12) had increased spinal latencies from both the L1 and L4 vertebral level sites of transcutaneous spinal stimulation consistent with slowed conduction in the pelvic efferent nerves innervating the intramural striated sphincter musculature in addition to slowed conduction in the perineal branch of the pudendal nerve innervating the periurethral component of the same sphincter musculature (Snooks and Swash, 1984a). All 12 patients had normal conduction in the innervation of the puborectalis and external anal sphincter muscles as shown by the results of spinal and pudendal nerve stimulation studies. However, seven patients had evidence of reinnervation in the external anal sphincter muscle, *i.e.* an increased single fibre EMG density (Neill and Swash, 1980) (Fig. 2). There were no significant differences between the resting and voluntary contraction anal canal pressures in the patients with stress incontinence of urine and the control subjects (Table 2).

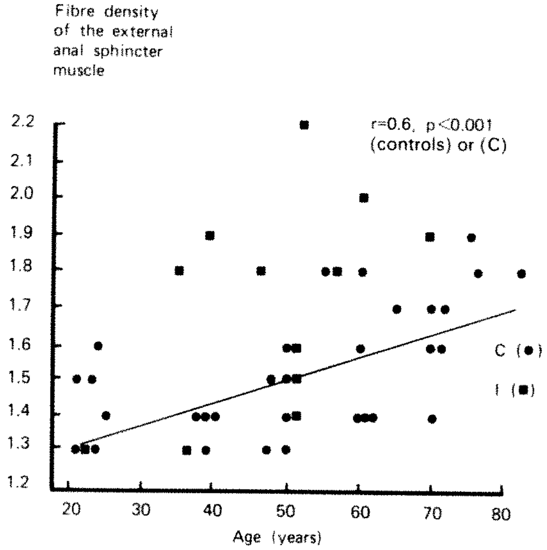

Fig. 2 Relationship of fibre density in the external anal sphincter muscle with age for control subjects (C) and patients with urinary incontinence (■).

Distal and proximal nerve latency correlations

In normal subjects the L1 spinal latency to the urethral striated sphincter musculature and the perineal nerve terminal motor latency are correlated ($r=0.54$, $P<0.05$) (Fig. 3), as are the pudendal and perineal nerve terminal motor latencies ($r=0.74$, $P<0.001$) (Fig. 4). However, in the 12 patients with stress urinary incontinence these correlations were lost (Figs 3 and 4).

Discussion

Slowing of perineal nerve conduction in patients with stress urinary incontinence is consistent with damage to the distal part of the nerve supply of the periurethral striated sphincter muscle. Damage to the pudendal nerve has been demonstrated in

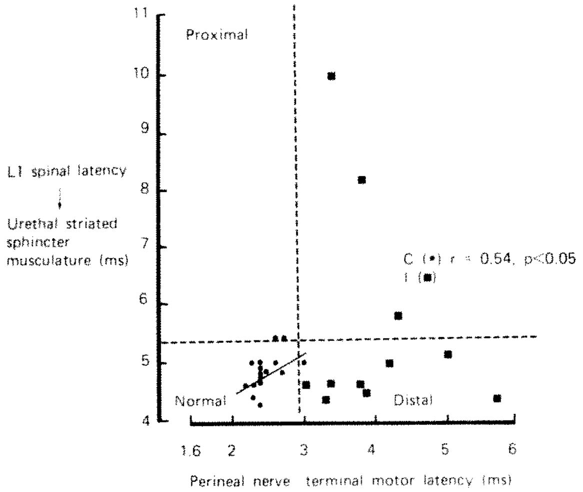

Fig. 3 Relationship of spinal and perineal latencies in control subjects (C) and patients with urinary incontinence (■). Eleven patients (■) are shown because the L1 spinal latency was unrecordable (Case number 5).

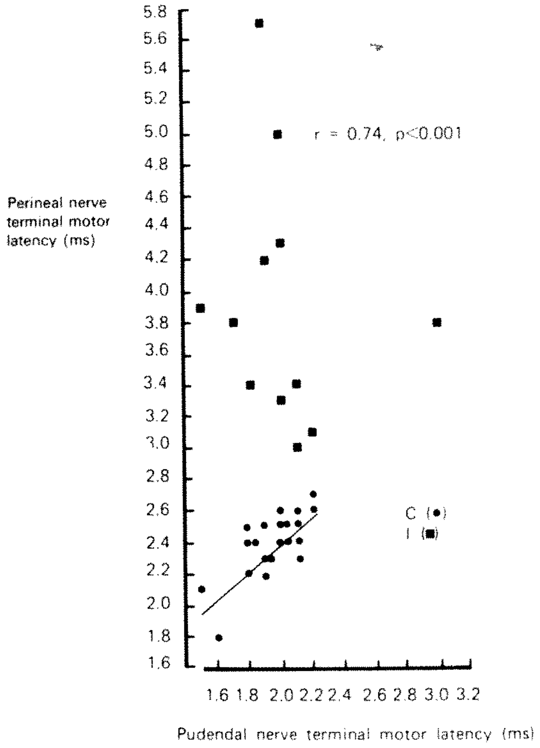

Fig. 4 Relationship of perineal and pudendal nerve terminal latencies in control subjects (C) and patients with urinary incontinence (■).

women after vaginal delivery (Snooks *et al.*, 1984b). This injury to the pudendal nerves is commonest in multiparae and women who have been delivered with forceps assistance, and is probably due to stretching of these nerves (Snooks *et al.*, 1984b). Eight of our 12 patients with stress urinary incontinence were multiparous and two had sustained forceps deliveries, both of whom became incontinent of urine after delivery (Table 1). In the majority of women, pudendal nerve dysfunction seen after vaginal delivery is reversible (Snooks *et al.*, 1984b) but in some patients, especially in multiparous women, the nerve damage progresses, leading to incontinence later in life (Parks *et al.*, 1977). This is thought to be due to stretch injury caused during perineal descent occurring when the patient strains at stool against a weakened pelvic floor (Henry *et al.*, 1982; Snooks *et al.*, 1985).

None of our 12 patients had evidence of slowed proximal (cauda equina) motor conduction, thereby excluding lesions of the cauda equina which could either predispose to or cause urinary incontinence. Transcutaneous spinal stimulation enables the innervation of both the intramural and of the periurethral striated sphincter musculature to be assessed. In two patients the motor latencies were increased after both L1 and L4 stimulation to the urethral striated sphincter musculature. This is consistent with slowed conduction in the pelvic efferent nerves innervating the intramural component as well as the periurethral component of the urethral striated sphincter musculature (Gosling, 1979).

Although conduction to the external anal sphincter muscle was normal, there was evidence of reinnervation in this muscle in some patients. This confirms the finding by Anderson (1984) that subclinical damage to the external anal sphincter muscle is present in many patients with stress incontinence of urine, as shown by our findings in patients with double incontinence (Snooks *et al.*, 1984a). Many of the latter patients complained of urinary incontinence before faecal incontinence developed; in these patients neurogenic damage to the puborectalis, external anal sphincter and urethral striated sphincter musculature was found (Snooks and Swash, 1984b; Snooks *et al.*, 1985).

Our findings suggest that damage to the nerve supply of the periurethral and sometimes also of the intramural striated muscle components of the urethral striated sphincter musculature is important in the pathogenesis of genuine stress incontinence of urine. This musculature supports the bladder neck and it is possible that some of the poor results of bladder neck reconstruction procedures (Stanton *et al.*, 1978) may be related to the relatively severe nerve damage that may be present. In order to restore urethral competence it may be necessary to bring down undamaged portions of the pelvic floor muscles into this region, as is done in the post-anal repair technique for faecal incontinence devised by Parks *et al.* (1977).

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The Authors

S. J. Snooks, FRCS, formerly The Sir Alan Parks Research Fellow, St Mark's Hospital. Now Senior Registrar in General Surgery, St Bartholomew's Hospital, London.

D. F. Badenoch, FRCS, Senior Urological Registrar, The London Hospital.

R. C. Tiptaft, FRCS, Senior Lecturer and Honorary Consultant Urologist, The London Hospital.

M. Swash, MD, FRCP, MRCPath, Director, Department of Physiology, St Mark's Hospital; Consultant Neurologist, St Mark's Hospital and The London Hospital.

Requests for reprints to: M. Swash, The Sir Alan Parks Physiology Unit, St Mark's Hospital, City Road, London EC1V 2PS.

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Adenomatous Metaplasia (Nephrogenic Adenoma) of Urothelium

An Analysis of 70 cases

T. F. FORD, G. M. WATSON and KATHARINE M. CAMERON

St Peter's Hospitals and Institute of Urology, London

Summary—A retrospective analysis of 70 cases of adenomatous metaplasia seen in the St Peter's Hospitals over a 15-year period has been carried out. The lesions occurred at all ages (7-81 years) and in both sexes (51 males, 19 females) and were found throughout the urinary tract from pelvis to urethra. In the pelvis and ureter the finding was usually an incidental one in association with stones or chronic inflammation; ulceration was a frequent accompaniment. Most vesical and urethral lesions followed a surgical procedure months or years previously, the patients re-presenting with haematuria or irritative bladder symptoms. The endoscopic appearances varied but there was often a striking correlation between the location of the lesions and the site of previous surgery. The association of adenomatous metaplasia with ulceration and previous surgery leads us to suggest that it is merely an unusual response to wound healing and attempts to treat it by diathermy resection are, therefore, likely to meet with limited success. Cystoscopic follow-up of persistent lesions gives no reason to suppose they are pre-malignant.

Urothelium may undergo proliferative and metaplastic changes in response to a variety of stimuli, notably chronic inflammation and irritation (Mostofi, 1954). One such change, described first by Davis in 1949 as a hamartoma of the urinary bladder, was subsequently designated "nephrogenic adenoma" by Friedman and Kuhlenbeck (1950), who noted the similarity of the lesion to renal tubules and suggested that it resulted from mesodermal potentialities of the urothelium.

Although more than 50 examples have now been reported in the literature, more recently under the title of "adenomatous metaplasia", the lesion is still regarded as a rarity, confined to the lower urinary tract, the origin and natural history of which remain uncertain. The fact that the condition is undoubtedly more common than reported cases would suggest (Davis, 1980) prompted this review.

Patients and Methods

Seventy patients with adenomatous metaplasia were seen between 1968 and 1983 and their pathological sections and hospital records have been reviewed. A further 23 cases were referred to the Department of Pathology for a histological opinion.

Results

Clinical features

Of the 70 examples of adenomatous metaplasia, 22 were sited in the renal pelvis, 7 in the ureter, 35 in the bladder and 6 in the urethra.

Renal Pelvis Adenomatous metaplasia of the urothelium of the renal pelvis was, without exception, an incidental finding noted during histological examination of nephrectomy or partial nephrectomy specimens. The indications for surgery are shown in Table 1. The male patient with tuberculosis had coincidental polypoid lesions in his bladder which were considered to be tubercles at cystoscopy but subsequently proved to be due to adenomatous metaplasia.

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Table 1 Location, Age and Sex Distribution and Associated Clinopathological Conditions in 70 Cases of Urothelial Adenomatous Metaplasia

Location	*Age range*	*Clinicopathological association*	*Numbers*	
			Male	*Female*
Renal Pelvis (22 cases)	9-67	Calculi	14	5
		Caliceal diverticulum		1
		Tuberculosis	1	1
Ureter (7 cases)	9-75	Transitional cell carcinoma	2	
		Tuberculosis	2	
		Neuropathic bladder	1	1
		Ureteric obstruction	1	
Bladder (35 cases)	8-80	Prostatectomy	7	
		Urethroplasty	4	
		Interstitial cystitis	2	4
		Transitional cell carcinoma	7	
		Tuberculous cystitis	2	1
		Recurrent infection	2	4
		Non-specific	1	1
Urethra (6 cases)	24-78	Urethral diverticulum		1
		Prostatectomy	2	
		Urethroplasty	3	
		Total	51	19

Ureter Five of the seven examples of adenomatous metaplasia in the ureter were incidental discoveries in nephroureterectomy specimens (Table 1). In two patients, however, the polypoidal nature of the adenomatous metaplasia was the source of pre-operative radiological diagnostic difficulty. The first was a 58-year-old man who had previously undergone total cystectomy and left nephroureterectomy for transitional cell carcinoma and was noted 3 years later to have several filling defects in his remaining ureter. The second was a 9-year-old Asian boy who presented with painless haematuria. Intravenous urography showed a lower ureteric stricture with filling defects in the dilated proximal portion. In each patient, when the affected segment of ureter was excised, histological examination showed the filling defects to be due to polypoid areas of adenomatous metaplasia.

Bladder Of the 35 cases of adenomatous metaplasia of the bladder, 33 were associated with either previous urethral or bladder surgery or significant and well defined coincidental disease (Table 1). The remaining two cases fell into an ill defined category in which the vesical urothelium showed evidence of chronic inflammation for which a specific cause could not be identified. In six patients the lesions were unsuspected prior to histological examination of biopsy or cystectomy specimens. In the other 29, they were noted at cystoscopy. Their appearance varied from flat (13) or raised (5) erythematous patches to papillary (7) or polypoidal (4) projections into the lumen. They were found anywhere in the bladder and sometimes as a generalised mucosal change.

Seven patients had undergone a transurethral (5) or retropubic prostatectomy (2) 1 to 12 years previously. They presented again because three had developed further outflow obstructive symptoms, two had symptoms due to urinary tract infection, one had further bladder calculi and one had haematuria. At cystoscopy, flat erythematous or papillary lesions were seen on the trigone in four instances, on the posterior wall in one and in diverticula in two.

Four patients had each undergone two or more urethroplasties 4 months to 4 years prior to the finding of adenomatous metaplasia in the bladder at cystoscopic follow-up. Two were children with post-traumatic strictures; in the two adults the strictures were gonococcal and post-prostatectomy in origin. All four had had long-term urethral and/or suprapubic catheter drainage. The lesions were noted on the anterior wall in one patient (who had had a suprapubic catheter), in a diverticulum in another and on the lateral and posterior walls in the remaining two.

Six patients, two of whom were men, had longstanding interstitial cystitis for which they had all had repeated hydrostatic dilatations before the diagnosis of adenomatous metaplasia. In three cases the diagnosis was made on a biopsy of a "suspicious" area while in the other three the lesion was an incidental finding in partial cystectomy specimens removed in the course of augmentation cystoplasty.

Seven male patients had transitional cell carcinomas. In one, a papillary lesion was found at the site of resection, 3 months before, of a non-invasive papillary tumour. The remaining six patients, five of whom had undergone multiple resections or fulgurations in the past, all had invasive, often high grade tumours for which four eventually underwent radical cystectomy while two received radical radiotherapy. Lesions noted at cystoscopy were invariably thought to be tumour recurrences or carcinoma *in situ*.

Three patients, who had received chemotherapy 3 to 5 years previously for urinary tract tuberculosis, presented with symptoms attributable to small contracted tuberculous bladders. Florid erythematous and polypoidal lesions were noted at endoscopy over the base of the bladder in two cases and as a generalised mucosal change in one. The endoscopic appearances were persistent in all and two patients eventually underwent augmentation cystoplasty.

Six patients (4 female, 2 male) with recurrent and well documented urinary tract infections had not previously undergone bladder surgery. One of them had had a nephrectomy for tuberculosis 25 years earlier. Three gave a previous history of upper tract stones, one had ureteric obstruction associated with vesical diverticula, and one had detrusor instability. All presented with one or more of the following symptoms: dysuria, frequency, urgency, suprapubic pain and haematuria. As well as the adenomatous metaplasia noted at cystoscopy, three had associated squamous metaplasia, two had cystitis follicularis and all had signs of chronic inflammation both endoscopically and histologically. Both the symptoms and the pathological changes were resistant to chemotherapy; one patient eventually underwent caecocystoplasty.

Finally, there were two patients in whom neither previous surgery nor urinary tract infection appeared to be an associated factor. One, a lady of 56 years, had a 9-year history of frequency, nocturia and recurrent episodes of "cystitis" and acute retention. An intravenous urogram showed bilateral hydroureters. At cystoscopy there was cystitis follicularis of the trigone and around both ureteric orifices; areas of raised erythema were present on the lateral wall of the bladder, which was of small capacity and scarred. Biopsy showed extensive squamous and adenomatous metaplasia. The patient eventually underwent total cystectomy and ileal loop diversion. Most of the bladder was lined by squamous epithelium with areas of adenomatous metaplasia. The second patient, a 68-year-old man, presented with a solitary episode of painless haematuria. At cystoscopy his bladder was seen to be trabeculated with a polypoid lesion on the posterior wall. Biopsy showed this to be florid adenomatous metaplasia associated with a chronic inflammatory cell infiltrate.

Cystoscopic follow-up from 1 to 12 years (average 4.8) was available in 24 of the 29 patients in whom the lesion was seen endoscopically. In nine patients no further lesions were noted after the initial biopsy and diathermy; in 15, however, they persisted for periods ranging from 1 to 10 years (average 5). Recurrent infection was present in 13 patients in the latter group but in only 2 of the 9 in whom the lesions did not recur. In no case has there been any evidence of malignant transformation.

One patient deserves further mention. A man, treated for 10 years for transitional cell carcinoma with fulguration and later intravesical chemotherapy, developed a small superficial area of adenocarcinoma in continuity with, and apparently arising from, transitional epithelium. It was resected. Subsequent random biopsies showed adenomatous and glandular metaplasia, severe atypia and carcinoma *in situ*. Cystourethrectomy was performed and on histological examination of the specimen there was still an area of adenomatous metaplasia but no evidence of adenocarcinoma. The occurrence of adenocarcinoma and adenomatous metaplasia in the bladder at different times was considered to be coincidental.

Urethra In one of the six patients, focal areas of adenomatous metaplasia were found incidentally in an infected periurethral diverticulum. Flat erythematous lesions were noted in the prostatic urethra in two patients following transurethral prostatectomy 1 and 6 years previously. In the remaining three patients, all of whom had undergone staged urethroplasties in the past, flat or papillary lesions were seen endoscopically at the site of the anastomoses.

Site of vesical and urethral lesions It has already been noted that adenomatous metaplasia may occur anywhere in the bladder. An attempt was made to correlate the site of the lesions to the associated pathology. Where prior surgery had been performed there was often a striking relationship between the location of the lesions and that of previous loss of urothelial continuity. For example, five of the seven lesions following a previous prostatectomy occurred on the trigone and bladder base; in two patients they were found at the site of resected bladder tumour, in one at the site of a long-term suprapubic catheter on the anterior wall and in three at the site of urethral anastomoses. In other instances urothelial ulceration (for example following hydrostatic dilatation or in association with infection) might reasonably be expected to occur and, indeed, is a frequent accompaniment of adenomatous metaplasia of the upper tract.

Pathology

As one would expect from the cystoscopic appearances, the histological lesion may be papillary,

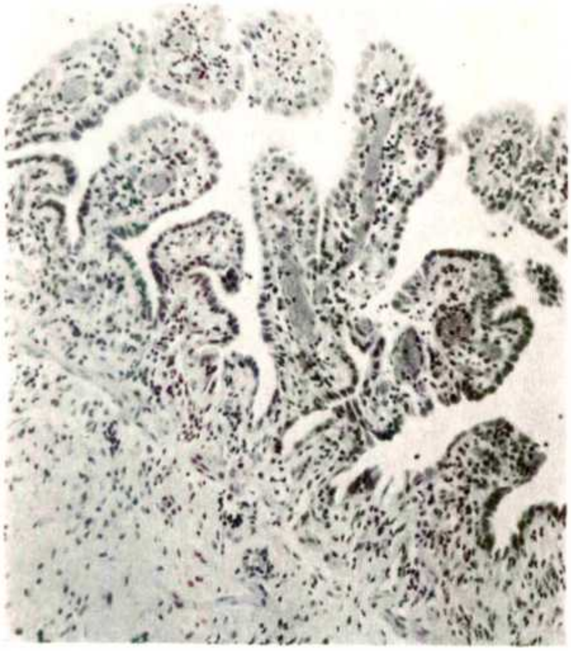

Fig. 1 Adenomatous metaplasia: a single layer of cuboidal epithelial cells covers papillary projections of the lamina própria. (H and E × 33. Enlargement × 3.4)

polypoidal or flat. In the renal pelvis, ureter and urethra a low polypoidal or flat surface is most common, while in the bladder all three types occur. Whatever the pattern, the surface is usually covered by a single layer of cuboidal or low columnar epithelial cells (Fig. 1). In addition, small tubular structures are usually present—in the cores of papillae in the papillary variety and in the true lamina propria in all three types (Fig. 2). The tubules may be well formed and lined by cells similar to those on the surface. Small cysts also occur and, especially in these, the lining epithelium may present a hobnail appearance. Tubule formation is less well defined in some cases and the lesion is composed of nests of cells with rather large, pale, vesicular nuclei, some of which have prominent nucleoli, and pale eosinophilic, sometimes vacuolated cytoplasm (Fig. 3). A degree of pleomorphism and even an occasional mitotic figure may be seen and lead to an erroneous diagnosis of invasive carcinoma. In these circumstances a basement membrane stain may help to demonstrate the tubular nature of the lesion. A further factor which may cause confusion with carcinoma is the occasional penetration of the tubules between superficial muscle bundles (Fig. 4).

An inflammatory infiltrate is invariably present. Squamous metaplasia is a common accompaniment—especially in the renal pelvis where, in addition, evidence of ulceration is usually seen. When situated on a papilla the lesion may be difficult to distinguish from collecting tubules (Fig. 5) but in the extrarenal pelvis it is easy to spot.

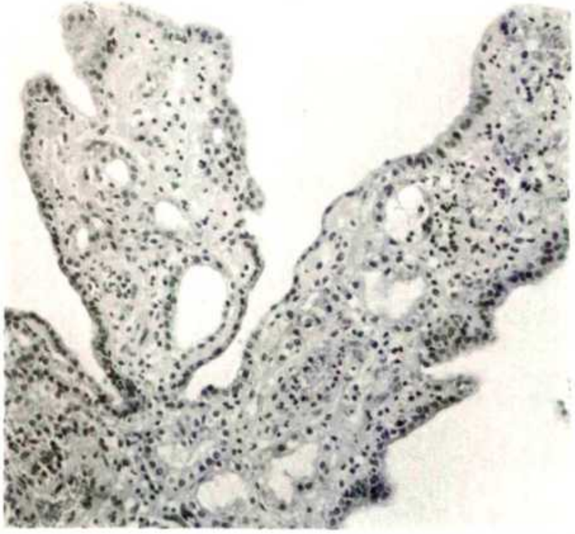

Fig. 2 Area of papillary adenomatous metaplasia: well formed tubules present in papillary cores and lamina propria. (H and E × 31. Enlargement × 3.1)

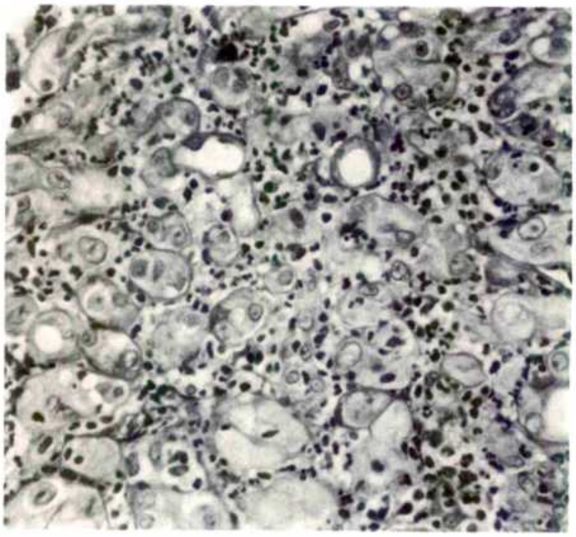

Fig. 3 Adenomatous metaplasia: ill-formed tubules in lamina propria lined by pleomorphic cells and outlined by a prominent basement membrane. An inflammatory cell infiltrate is present. (PAS × 77. Enlargement × 3.1)

Discussion

There have been isolated reports of adenomatous

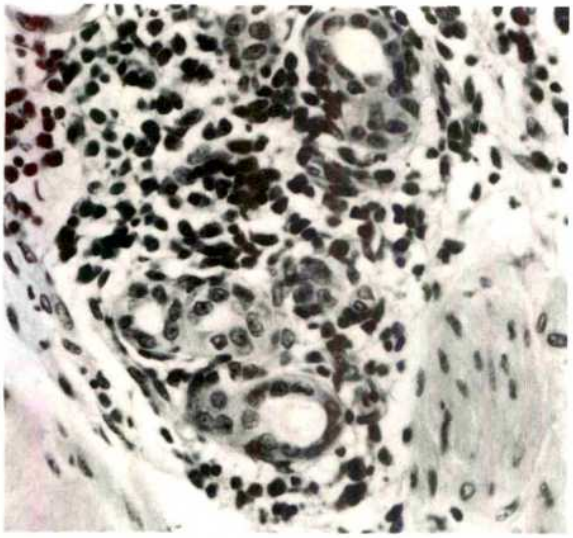

Fig. 4 Adenomatous metaplasia: tubules penetrating between superficial muscle bundles. (H and E × 77. Enlargement × 3.1)

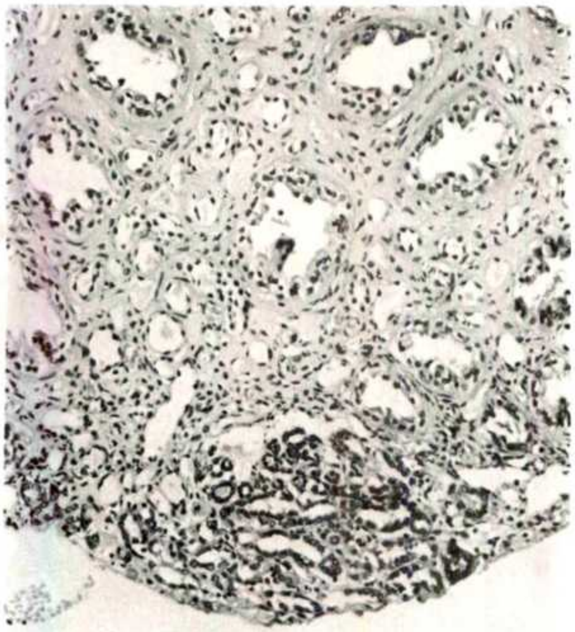

Fig. 5 Focus of adenomatous metaplasia at tip of renal papilla. (H and E × 33. Enlargement × 3.4)

metaplasia affecting the ureter (Jakse and Mikuz, 1983) and urethra (Peterson and Matsumoto, 1978; Berger *et al.*, 1981); these, together with the cases in the present series, make it clear that this reaction represents the potential of the urothelium as a whole to undergo an unusual form of metaplasia. The term "nephrogenic adenoma" should not be used (Sussman *et al.*, 1974; Molland *et al.*, 1976) since the lesions clearly arise from any part of the urothelium, whether of mesodermal or endodermal origin. Furthermore, electron microscopic studies have shown that the tubules bear little ultrastructural resemblance to renal elements (Imahori and Magoss, 1980; Raghavaiah *et al.*, 1980; Bhagavan *et al.*, 1981; O'Shea *et al.*, 1981).

What is not clear is the precise stimulus for the response. Urinary tract stones, prostatectomies, long-term catheterisation, hydrostatic dilatations, resection and fulguration of bladder tumours, tuberculous and other chronic inflammatory processes all damage the urothelium. The correlation between the location of the adenomatous metaplasia and the site of previous loss of urothelial continuity in this series has already been mentioned. There are 33 well documented reports of vesical adenomatous metaplasia in the world literature, in 24 of which there was a history of previous bladder surgery or trauma. It is interesting to relate the precise location within the bladder of the metaplastic change to the site of surgery or trauma (Table 2). Not only is the correlation good (for example, in terms of laterality), but in no instance has the adenomatous lesion developed where incision or trauma might not reasonably have been expected to breach the epithelium. It is suggested that adenomatous metaplasia may thus occur as a metaplastic response of the uretholium during repair. The regenerating epithelium appears to form a single layer with a tendency to invaginate and proliferate in the subepithelial tissues. This process may be analogous to the deep epithelial heterotopia described in a healing chronic peptic ulcer (Taylor, 1927) and is similar to the mesothelial proliferation and sequestration seen in the wall of an infected hydrocele.

What then is its natural history? In both the present study and in reported cases the lesion is often an incidental finding and, following initial biopsy, resection or diathermy, frequently does not recur (Hasen, 1962; Sussman *et al.*, 1974; Gordon and Kerr, 1975; Kaswick *et al.*, 1976; Tannenbaum *et al.*, 1980). By contrast, some of the reported lesions not only recurred but frequently progressed after transurethral resection (Friedman and Kuhlenbeck, 1950; Kalloor and Shaw, 1974; Taneja *et al.*, 1974; Molland *et al.*, 1976; O'Shea *et al.*, 1981). Such an extension may be anticipated if the lesion really is a response to epithelial damage. In the present series, recurrences have been recorded in 15 patients over periods of up to 12 years and it is

Table 2 Location of Vesical Adenomatous Metaplasia in Relation to Previous Surgery or Trauma

Location	*Surgery or trauma*	*Source*
Trigone	Y-V/plasty bladder neck	Kaswick *et al.* (1976)
	Rupture prostatic urethra	Kaany and Werner (1974)
	Suprapubic cystostomy	O'Shea *et al.* (1981)
	TURP and catheterisation	Goldman (1972)
	Bladder diverticulectomy	Taneja *et al.* (1974)
Right lateral wall and right ureteric orifice	Gunshot wound to right side of bladder	Imahori and Magoss (1980)
	Suprapubic prostatectomy	Berger *et al.* (1981)
	TUR bladder neck + bilateral ureteric implants	Christoffersen and Møller (1972)
	TURP	Sussman *et al.* (1974)
	Right ureteric implant	Raghavaiah *et al.* (1980)
	Right uretero-neocystostomy	Gordon and Kerr (1975)
Left lateral wall and left ureteric orifice	Ruptured urethra and suprapubic cystostomy	Allan (1975)
	Multiple resections TCC	Sussman *et al.* (1974)
	Left uretero-neocystostomy	Behesti and Morales (1982)
	Left uretero-ileo-cystostomy	Kaswick *et al.* (1976)
Posterior wall	Bilateral ureteric reimplants	O'Shea *et al.* (1981)
	Bilateral ureteric reimplants	Leonard *et al.* (1976)
	Urethral catheter	Goldman (1972)
Dome	Suprapubic prostatectomy	Berger *et al.* (1981)
	Intraperitoneal rupture of bladder	Hasen (1962)
	Suprapubic cystostomy	Sussman *et al.* (1974)
Generalised	TUR right ureterocele + bilateral reimplants	Berger *et al.* (1981)
	TURP + suprapubic cystostomy	Berger *et al.* (1981)

interesting to note that recurrent infection (including tuberculosis) was present in all but two. In some cases of adenomatous metaplasia in which the lesion has progressed despite repeated transurethral resections, cystectomy has been necessary because of increasing frequency, dysuria and suprapubic pain (Allan, 1975; Molland *et al.*, 1976). The striking appearance of the lesion at cystoscopy makes it easy to assume that it is responsible for the symptoms but it is quite possible that both the symptoms and the adenomatous metaplasia are the result of the underlying "inflammatory" conditions. After all, cystectomy is not infrequently performed for the progressively contracting bladder of uncertain aetiology in which no adenomatous metaplasia is present.

The question as to whether adenomatous metaplasia can be a pre-malignant condition must remain unanswered. There is one well documented case of a tuberculous bladder, containing areas of adenomatous metaplasia, which subsequently developed an adenocarcinoma (Molland *et al.*, 1976). Malignant change was described in one of the cases reported by Christoffersen and Møller (1972) because of "signs of invasive growth predominantly of acinar character with atypical epithelium". As has already been pointed out, however, cellular atypia and muscle penetration may be seen in adenomatous metaplasia *per se* and it may be significant that this "tumour" did not recur after resection and electrocoagulation. In the one case in the present series in which a diagnosis of vesical adenocarcinoma preceded that of adenomatous metaplasia, the lesions were considered to be coincidental. In none of our patients with lesions recurring over periods of up to 12 years has malignancy supervened.

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The Authors

T. F. Ford, MA, DM, MCh, FRCS, formerly Senior Registrar in Urology, St Peter's Hospitals. Now Senior Registrar in Urology, Royal United Hospital, Bath.

G. M. Watson, FRCS, MRC Research Fellow, Institute of Urology.

Katharine M. Cameron, BSc, MB, FRCPath, Senior Lecturer in Pathology, Institute of Urology.

Requests for reprints to: T. F. Ford, Department of Urology, Royal United Hospital, Combe Park, Bath BA1 3NG.

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Chemotherapy before Radiotherapy for T3 Bladder Cancer.

A Pilot Study

S. B. KAYE, J. R. MacFARLANE, I. McHATTIE and A. J. L. HART

Departments of Urology, Radiotherapy and Oncology, Western Infirmary and Gartnavel General Hospital, Glasgow

Summary—Seventeen patients with stage T3 bladder cancer were treated in a pilot study of initial chemotherapy (four courses of cyclophosphamide, methotrexate and 5-fluorouracil) followed by megavoltage radiotherapy 6000 cGy) to the bladder. Chemotherapy was well tolerated and did not lead to any increase in toxicity from the radiotherapy.

Assessment of response in all cases was not possible because of the variable extent of the initial biopsy. Of the 12 patients in whom assessment was possible, there was no objective change in 9 (4 cases of T3a; 5 cases of T3b) and there was objective evidence of disease progression in 3 (2 cases of T3a; 1 case of T3b).

Thirteen patients have now died and the median survival for patients in this study was 27 months, with a 3-year survival rate of 26%. Three patients died with recurrence in the pelvis, 5 with both local and metastatic disease, 2 with metastases only, and 3 from other causes.

These data indicate that this particular form of chemotherapy given as initial treatment for T3 bladder cancer does not appear to lead to an improvement in the results obtainable from radiotherapy alone.

The prognosis of patients with invasive bladder cancer is poor, with at least 60% dying within 5 years whichever combination of radiotherapy and surgery is used as primary treatment (Bloom, 1979). A range of cytotoxic drugs has been demonstrated to have some efficacy in advanced bladder cancer, although response rates, even for combination chemotherapy, do not generally exceed 50%, and no survival benefit in such patients has yet been proven (Yagoda, 1980). Nevertheless, complete remissions are occasionally seen and it is therefore reasonable to hope that the addition of chemotherapy to the initial treatment programme will improve results. By treating with chemotherapy prior to radiotherapy, an early attack on micrometastatic disease is attempted and, in addition, any shrinkage in the local tumour might render local irradiation more effective.

Among the drugs with demonstrable single agent activity in advanced bladder cancer are cyclophosphamide, methotrexate and 5-fluorouracil. The overall response rate claimed for cyclophosphamide from two reports (50 patients) is 26% (Merrin *et al.*, 1975; Yagoda *et al.*, 1977), although a lower figure might now be obtained using stricter modern criteria. Similarly, an overall response rate of 39% was quoted for 5-fluorouracil in a review of 56 patients (de Kernion, 1977), but it is doubtful if this would be reproduced using current response criteria. For methotrexate, responses have been reported using a variety of schedules, with no apparent advantage for high dose treatment. The largest series are those of Turner *et al.* (1977), comprising 61 patients, and Natale *et al.* (1981), comprising 42 patients, and the overall response rate for these studies was 33%. It should be noted, however, that in all cases response rates related to metastatic or recurrent disease, and there is no in-

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formation on the sensitivity of untreated primary invasive bladder cancer to these drugs.

Nevertheless, the use of the three-drug combination of cyclophosphamide, methotrexate and 5-fluorouracil in other diseases (particularly breast cancer) is widespread (Canellos *et al.*, 1974) and in view of their reported activity as single agents in bladder cancer it seemed logical to assess this particular combination in invasive carcinoma of the bladder prior to conventional treatment with radiotherapy. A pilot study was therefore set up to assess the initial treatment of T3 bladder cancer (following initial biopsy) with four courses of cyclophosphamide, methotrexate and 5-fluorouracil (CMF), followed by radical radiotherapy, and to assess any obvious effect on response and survival.

Patients and Methods

Seventeen patients with invasive bladder cancer were included in this study; there were 12 men and 5 women (mean age 63.8 years, range 44–79). Ten patients were clinically assessed prior to therapy as having stage T3a disease and 7 as stage T3b. Before starting treatment all patients had undergone cystoscopy, biopsy and bimanual examination, as well as ultrasound examination of the bladder, chest X-ray and bone scan.

Chemotherapy comprised cyclophosphamide 500 mg, methotrexate 100 mg, and 5-fluorouracil 500 mg. All were given as an intravenous bolus injection every 3 weeks, followed by folinic acid at 24 h, 15 mg qds orally for 2 days. Four courses were given following initial biopsy.

Reassessment was made after four courses by means of repeat cystoscopy, bimanual and bladder ultrasound examination, chest X-ray and bone scan. All patients except 2 then received a course of megavoltage radiotherapy to the pelvis, comprising a total tumour dose of 6000 cGy to the bladder in 30 fractions over 6 weeks. The dose delivered was 4000 cGy over 4 weeks in 2 patients who were considered too unfit to complete the radical course.

Reassessment was performed after radiotherapy. In 10 cases, chemotherapy (CMF as above) was continued once every 3 months after radiotherapy. Three patients underwent salvage cystectomy for residual tumour, while no further treatment was given to the remainder until progressive disease occurred.

Results

Toxicity

Chemotherapy was well tolerated and side effects were limited to nausea (5 patients), cystitis (3) and diarrhoea (1). No treatment-related myelosuppression was noted. All of these side effects were mild and subsided following cessation of chemotherapy, and no patient had to have his chemotherapy modified or stopped.

Radiotherapy was associated with occasional nausea and diarrhoea, but the side effects were no more severe in this study than have been seen previously in patients receiving radiotherapy alone.

Response

Symptoms Of the 17 patients entered, 5 underwent extensive resection of tumour at the initial biopsy. Although these patients did report symptomatic benefit following chemotherapy, it was not possible to attribute this solely to chemotherapy. One other patient reported clear symptomatic improvement, although there was no objective evidence of response. In only one case was there evidence of worsening of symptoms; in the remaining patients no change in symptoms was reported.

Objective response

T3a Disease Of the 10 patients with T3a tumours, 4 underwent extensive resection at the initial biopsy. A repeat ultrasound examination prior to chemotherapy was not then performed. After chemotherapy, cystoscopy and bimanual examination revealed no evidence of tumour in 3 patients. Residual tumour was detected in the fourth case. In the remaining 6 cases there was no evidence on ultrasound, bimanual examination or cystoscopy of a response to chemotherapy. In 4 of these cases ultrasound, cystoscopy and bimanual examination were unchanged, and in 2 cases ultrasound and cystoscopy indicated disease progression (clearly progressive on bimanual examination in one).

T3b Disease Of the 7 patients with T3b disease, 1 patient underwent extensive initial resection although residual tumour was visible at repeat cystoscopy after chemotherapy. In the remaining 6 cases there was no evidence of response to chemotherapy on ultrasound examination, bimanual examination or cystoscopy. Clear progression in all three parameters was reported in 1 case and no change was reported in the other 5.

Survival

Of the 17 patients entered, only 4 are still alive at 31, 41 and 55 months (2 cases) after diagnosis. These include 3 patients with T3a and 1 with T3b disease. The median survival for the whole series was 27 months from diagnosis. The survival curve life table is seen in the Figure.

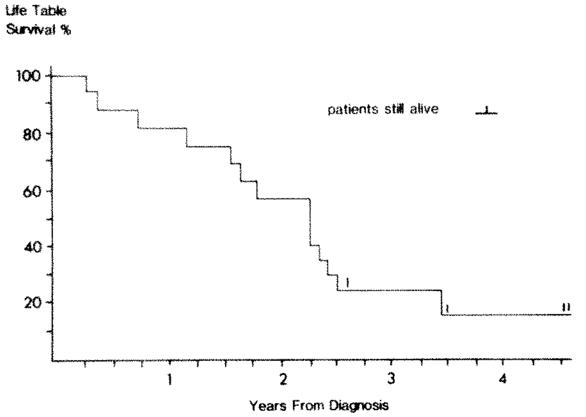

Fig. Life table survival for 17 patients treated with CMF prior to radiotherapy.

Of the 13 patients who died, 5 had evidence of both local and metastatic disease at the time of death. Three had evidence of recurrent disease in the pelvis only and 2 had evidence of metastatic disease only. Of the 3 others, the cause of death in one case was massive pulmonary emboli following a salvage cystectomy for recurrent tumour (no metastatic tumour being present at post mortem); in a second case the cause of death was myocardial infarction (no bladder tumour present at post mortem), while the cause of death in the third patient, who had clinically evident recurrence, was probably self-poisoning.

Discussion

This study highlights the difficulties of assessment of response to initial chemotherapy in patients with T3 bladder cancer. In future studies serial CT scans using new generation CT scanners might well be a useful addition to the methods reported here, with the baseline scan performed immediately after the initial biopsy. Despite these difficulties it is possible to draw several conclusions from this study.

Firstly, the approach of chemotherapy before radiotherapy is feasible and does not add to the toxicity of radiotherapy. Secondly, this particular drug combination is unlikely to yield an improvement in results, since the survival data are no better than those which might be achieved using radiotherapy alone. Thirdly, the pattern of relapse in these patients suggests that the addition of chemotherapy in this form does not contribute to control either of local or metastatic disease. Fourthly, it is possible to conclude that the reason for these disappointing results is intrinsic insensitivity of bladder cancer to cytotoxic drugs. However, it remains conceivable that other drugs or combinations of the new cytotoxic drugs may prove more effective as initial treatment.

A small study reported by Clyne *et al.* (1983) comprised 12 patients given Adriamycin and 5-fluorouracil prior to radiotherapy for T3 bladder cancer. Although assessment of response to initial chemotherapy was not reported, 6 patients failed overall to show any tumour regression and 5 developed distant metastases. Survival was no better than that of a retrospective series treated with radiotherapy alone.

More recently, however, cisplatin has shown some promise in the treatment of advanced bladder cancer (Yagoda, 1979) and the combination of methotrexate and cisplatin is receiving increasing attention in phase III studies (Kaye *et al.*, 1984). Cisplatin has already been used as a single agent in the initial treatment of invasive bladder cancer by Raghaven *et al.* (1984). In a series of 50 patients with measurable invasive bladder cancer they reported an objective response rate in the primary tumour of 70% following two courses of cisplatin (100 mg/m^2), with symptomatic improvement in 76%. Response was assessed by repeat cystoscopy, bimanual examination and CT scan. Following chemotherapy, patients went on to radiotherapy and/or surgery and the actuarial survival rate at 2 years was 82%.

Another study involving a smaller number of patients has recently been reported by Fagg *et al.* (1984) regarding the use of cisplatin as initial treatment for invasive bladder cancer. Among 17 patients, 11 objective responses were recorded after three doses of cisplatin (100 mg/m^2), although there were no complete responses. The study emphasised the importance of objective assessment of response using serial CT scans to calculate reductions in tumour volume.

These results are encouraging and further information is now clearly required regarding the sensitivity of primary invasive bladder cancer to systemic chemotherapy. It would be particularly important to compare this information with data already available on the sensitivity of metastatic disease.

It therefore remains possible that drug combinations such as methotrexate and cisplatin may yield more encouraging results in the initial treatment of invasive bladder cancer than those reported in this study.

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The Authors

S. B. Kaye, MD, MRCP, Senior Lecturer, Department of Oncology, University of Glasgow.

J. R. MacFarlane, FRCSE, formerly Senior Registrar, Department of Urology, Southern General Hospital, Glasgow. Now Consultant Urologist, Victoria Hospital, Kirkcaldy.

I. McHattie, FRCR, Consultant Radiotherapist, Western Infirmary, Glasgow.

A. J. L. Hart, FRCSE, formerly Senior Registrar, Department of Urology, Western Infirmary, Glasgow. Now Consultant Urologist, East Glamorgan Hospital, Pontypridd.

Requests for reprints to: S. B. Kaye, Department of Oncology, University of Glasgow, 1 Horselethill Road, Glasgow G12 9LY.

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Vesico-uterine Fistula

G. C. ILOABACHIE and O. NJOKU

Department of Obstetrics and Gynaecology, University of Nigeria Teaching Hospital, Enugu, Nigeria

Summary—Nine cases of vesico-uterine fistula caused by injury to the bladder at Caesarean section or by rupture of the uterus and bladder following obstructed labour are described.

Symptoms depend on the level of the lesion, menstruation into the bladder and menouria occurring when the fistula is above the internal cervical os: whatever the level, most patients with vesico-uterine fistula present with incontinence of urine.

A transperitoneal approach appears to give better results than a transvesical repair.

Most fistulas between the bladder and the genital tract following delivery are communications between the bladder and the vagina. Vesico-uterine fistulas are much less common and occur when the uterus has been breached either by rupture in labour or by Caesarean section.

Patients and Methods

Of the 840 patients operated upon for bladder fistula over the 10-year period 1973 to 1983 there were nine cases of vesico-uterine fistula, an incidence of about 1 in 100.

Seven of the nine patients were referred from other hospitals with a diagnosis of vesico-vaginal fistula and two patients developed fistulas after Caesarean sections performed at the University of Nigeria Teaching Hospital, Enugu.

Three patients had obstructed labour with rupture of uterus and bladder and six had Caesarean sections.

Presenting features

Commonly observed were ammoniacal odour, vulval wetness and ammoniacal dermatitis. The onset of incontinence was immediate in all patients. Four had cyclical haematuria due to menstruation via the bladder and they were also incontinent of urine (unlike the patients with menouria described by Youssef (1957), who were not incontinent).

Amenorrhoea occurred in two patients who were incontinent and did not have menouria. Two patients were incontinent but also voluntarily passed small quantities of urine *per urethram*.

Diagnosis

Speculum examination of the vagina did not demonstrate vesico-vaginal fistulas but there was urinary incontinence through the cervical os.

Intravenous urograms showed contrast escaping into the vagina but were of no value in differentiating between vesico-vaginal and vesico-uterine fistulas. At examination under anaesthesia, instillation of dilute methylene blue into the bladder through the urethra confirmed the presence of vesico-uterine fistulas in all nine cases, because the dye appeared in the vagina through the cervical os.

The vesico-uterine fistulas observed at operation involved the cervical canal below the internal os in four cases, and in three cases both the cervix and the isthmus were involved. In the remaining two cases the fistulas involved the lower portion of the corpus uteri and the isthmus and were wholly above the internal os.

Treatment and Results

Injuries to the bladder discovered at Caesarean section or at laparotomy for ruptured uterus should be immediately repaired. The repair of other bladder fistulas, especially when caused by pressure necrosis, should be delayed for at least 3 months. This allows time for sloughs to separate, inflammation to subside and improvement of local vascular

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supply to occur (Falk and Tancer, 1956; Lawson, 1977).

Urethral catheter drainage may result in the spontaneous closure of small fistulas (Lawson, 1977; Grasiotti *et al.*, 1978). In larger fistulas significant reduction in size may occur, with or without the catheter drainage. Meanwhile the general management should consist of improved nutrition, correction of anaemia, treatment of urinary and other intercurrent infections and maintenance of morale.

Table Outcome of operative repair of the fistula

Method of repair	*No. of patients*	*Successful*
Transperitoneal	6	6
Transvesical	3	1

The definitive treatment is surgical closure of the fistula. The abdominal approach is to be preferred because vesico-uterine fistulas are not accessible vaginally. Of the nine cases described in this paper, six were successfully repaired transperitoneally. Of the three repaired transvesically, two failed but were subsequently successfully closed transperitoneally (Table).

Discussion

Urinary incontinence of obstetric origin continues to be a major gynaecological problem in Nigeria. Most of the fistulas are vesico-vaginal and are caused by ischaemic necrosis resulting from prolonged obstructed labour (Lawson and Stewart, 1970). The fistulas under review were, however, caused either by injury to the bladder at Caesarean section or by simultaneous rupture of the uterus and bladder following obstructed labour. If injury to the bladder is unrecognised or inadequately treated, incision or damage to the uterus completes the cycle for a vesico-uterine fistula (Lawson and Stewart, 1970).

The main symptom of vesico-uterine fistula is urinary incontinence, often occurring immediately after Caesarean section or laparotomy for ruptured uterus. This distinguishes it from other bladder fistulas resulting from pressure necrosis in which incontinence is delayed for a few days. Vesico-vaginal fistulas are not found on vaginal examination; the dye test confirms urinary incontinence occurring through the cervical os. If the dye does not come through the cervical os, a uretero-vaginal (ureteric) fistula must be excluded.

The classical syndrome of amenorrhoea, menouria and urinary continence described as characteristic of vesico-uterine fistulas (Youssef, 1957; Sammour, 1970) has not been encountered in this hospital. It would appear that the symptoms relate to the level of the lesion. When it is above the interal os menouria may occur: when below it, urinary incontinence results.

The two patients who were incontinent and had menouria but passed small quantities of urine *per urethram* represented the cases in which the lesion occurred at the level of the isthmus and the lower part of the corpus uteri.

Although transvesical repair is preferred by Mack (1969) and Lawson (1972), in our hands the transperitoneal approach gave the best results as it provided improved exposure of the fistulous tract between the bladder and the uterus.

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The Authors

G. C. Iloabachie, MRCOG, FWACS, FMCOG, Senior Lecturer and Consultant.

O. Njoku, MB, BS(Nig), Senior Registrar.

Requests for reprints to: G. C. Iloabachie, Department of Obstetrics and Gynaecology, University of Nigeria Teaching Hospital, Enugu, Nigeria.

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Prostatic Ultrasonography: a Useful Technique?

C. KADOW, J. C. GINGELL and J. B. PENRY

Departments of Urology and Radiology, Southmead Hospital, Bristol

Summary—Two hundred and forty-four transrectal prostatic ultrasonograms have been reviewed and the findings compared with the final pathological or clinical diagnosis. A high degree of accuracy was achieved in diagnosing benign prostatic hyperplasia.

Ultrasonography proved invaluable in staging proven prostatic carcinomas but it was disappointing as a primary diagnostic tool for cancer, with false positive and negatives rates of 12 and 31% respectively. These findings are discussed in the light of other workers' results.

Further applications for prostatic ultrasonography are outlined.

Transrectal ultrasonography is a simple, non-invasive method for imaging the prostate gland. Since Watanabe *et al.* (1975) published their results, enthusiasm for the technique has increased and technical advances in ultrasonics have kept pace with this increase, so that we now possess sophisticated machines capable of demonstrating fine details of the echo patterns in the substance of the gland. With the aid of computerisation we can calculate accurately the volume and weight of the prostate pre-operatively. Ultrasonography allows more accurate T-category assessment of prostatic cancer than was hitherto possible and its potential role in the early diagnosis of localised prostatic tumours has been keenly anticipated.

We have used transrectal ultrasonography for the past 3 years in the investigation of prostatic disease and we present our experience with this imaging technique.

Patients and Methods

Since June 1981, transrectal prostatic ultrasonograms have been performed in this hospital using the Aloka chair fitted with a 3.5 mHz transducer in a rotating transrectal probe interfaced to a Philips Sono-Diagnost B 7100 console. The indications for transrectal scanning were symptoms of bladder outflow obstruction in the majority of patients, though some had perineal pain, dysuria or suspected malignancy on rectal examination. Patients were asked to attend with a full bladder. The rectal probe was covered with a water-filled rubber balloon to provide better sonar contact and to protect the rectal mucosa. The balloon was lubricated and when the patient was seated comfortably with the probe in his rectum, it was raised vertically to a height of 10 cm. In most patients this was just above the level of the prostate gland. Serial 360° radial scans were performed and recorded on X-ray film as transverse tomograms of the prostate at 0.5-cm intervals as the probe was lowered. All ultrasonic scans were interpreted by the same radiologist (J.B.P.) and ultrasonic diagnosis was correlated with subsequent histological and cytological findings where possible.

Results

The prostate was not seen in 15 patients; this was due to technical failure in most cases but patient non-acceptance accounted for four failures. Of 20 glands reported as ultrasonically normal, 5 had benign hyperplasia and 2 carcinoma (Table 1). Benign prostatic hyperplasia (BPH) was diagnosed accurately in 104 of 125 cases (75.9%). Prostatic cancer was diagnosed correctly in 53 of 74 cases (67.5%). Nearly all cases of prostatitis were correctly identified.

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Table 1 Results of Ultrasonography

		Final Diagnosis				
Ultrasonic diagnosis	*Number of cases*	*Number of cases Normal*	*BPH*	*Carcinoma*	*Prostatitis*	*Other*
Normal	20	12	5	2	1	—
BPH	125	—	104	18	1	2*
Carcinoma of prostate	74	—	16	53	1	2/2*
Prostatitis	5	—	—	—	4	1*
Other	3	—	—	—	—	3
Technical failure	15	—	9	5	—	1*
Records missing	2					

* Records incomplete.

In 78 cases of histologically proven cancer (Table 2), the examination was technically unsatisfactory in 5 and in 21 an erroneous diagnosis was made on ultrasound. This represented an overall failure to detect cancer in 31% of cases.

Twenty-two cases of BPH were incorrectly labelled on ultrasound, 16 of those as cancer, giving a false positive rate for cancer of 12%.

Table 2 Detection Rates of Ultrasonography

Histological diagnosis (No.)	*Ultrasound correct (No.)*	*Ultrasound incorrect (No.)*	*Ultrasound technical failure (No.)*
Carcinoma (78)	52	17 (BPH) 3 (Normal) 1 (Prostatitis)	5
BPH (133)	101	16 (Carcinoma) 5 (Normal) 1 (Prostatitis)	9

Discussion

The examination was well tolerated by nearly all patients. Technical failures occurred early in the series when the operators were relatively unfamiliar with the equipment and technique. Patient non-compliance accounted for very few failures. Imaging was sometimes inadequate in patients in whom the distance from the buttocks to the base of the prostate exceeded 10 cm.

The ultrasonic features of benign prostatic hyperplasia have been well described by other workers and were seen consistently in our series (Fig. 1). They consisted of an increase in both the anteroposterior and transverse diameters of the gland and a change to a round or ovoid outline compared with the normal gland (Fig. 2). A prominent middle lobe or a large central adenoma was often seen clearly demarcated from surrounding tissue. Since the changes of BPH are fairly gross, the degree of accuracy in diagnosing this condition was high. This is in agreement with most published reports (Watanabe *et al.*, 1975; Brooman *et al.*, 1981; Braeckman and Denis, 1983; Miyazaki *et al.*, 1983). BPH is easily diagnosed on digital examination and ultrasound offers few advantages over this apart from the opportunity to diagnose T0 tumours pre-operatively (Brooman *et al.*, 1981) and the ability to assess prostatic size more accurately.

Locally advanced prostatic carcinoma was usually obvious both clinically and on ultrasound, but two patients in whom no prostate could be identified ultrasonically had advanced prostatic cancer. We feel that there is no useful diagnostic information to be gained from ultrasonography in patients with clinically obvious T3/4 tumours.

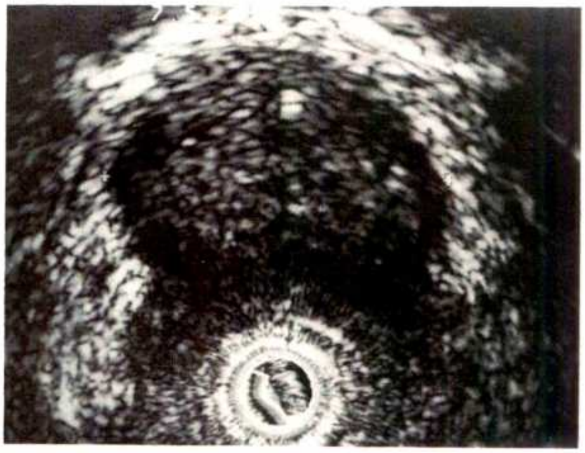

Fig 1 Benign prostatic hyperplasia; large central adenoma.

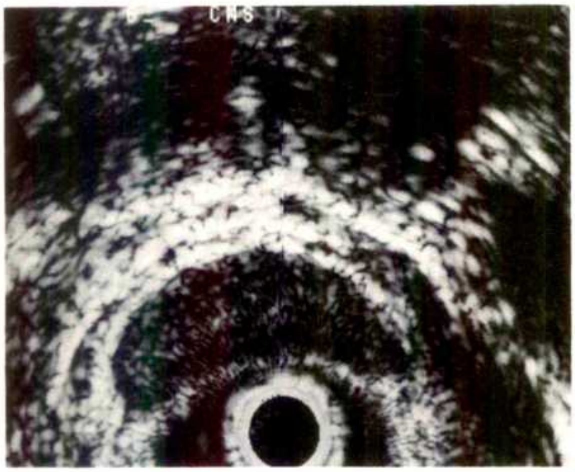

Fig. 2 Normal prostate. Note semilunar outline and homogeneous internal echo pattern. (Reproduced by kind permission of the Editor-in-Chief, Medicamundi).

Several tumours which had been staged as confined to the gland on digital palpation were found to have spread through the capsule on ultrasound, *i.e.* they had been understaged clinically (Fig. 3). In most cases an anterior or anterolateral capsular penetration had occurred. We are in total agreement with other workers that ultrasonography remains unsurpassed as a method for accurate T-category staging of proven prostatic carcinomas. In locally very advanced tumours, CT scanning may provide more accurate information about the extent of spread and is therefore more useful as an aid to planning radiotherapy (Mamtora *et al.*, 1981).

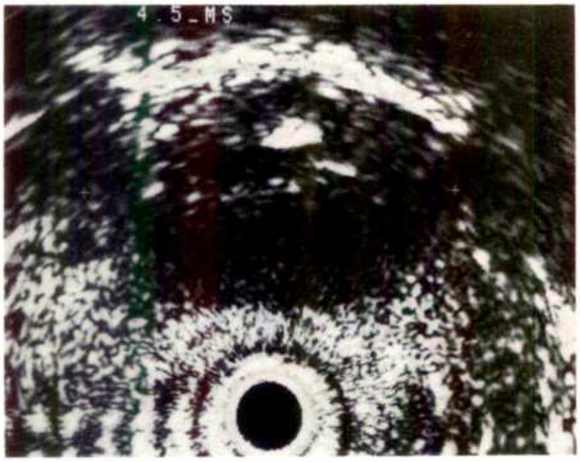

Fig. 3 T3 carcinoma of prostate. Anterolateral capsular penetration by tumour (+).

With early prostatic cancer problems arise. Focal tumours where a distinct nodule is present may be diagnosed fairly accurately, especially if the examination is combined with careful digital palpation (Figs 4 and 5). Diffuse early tumours may resemble BPH or prostatitis ultrasonically (Fig. 6) and a high clinical index of suspicion is required. We were unable to predict the presence of any T0 tumours pre-operatively, an experience we share with others (Braeckman and Denis, 1983). However, Brooman *et al.* (1981) were able to identify 11 of 13 T0 cancers accurately. It would seem therefore that with a very high index of suspicion, careful attention to scanning technique and accurate biopsy, the success rate for diagnosing early cancer may improve. Detailed analysis of the ultrasonic signals to allow accurate tissue characterisation and

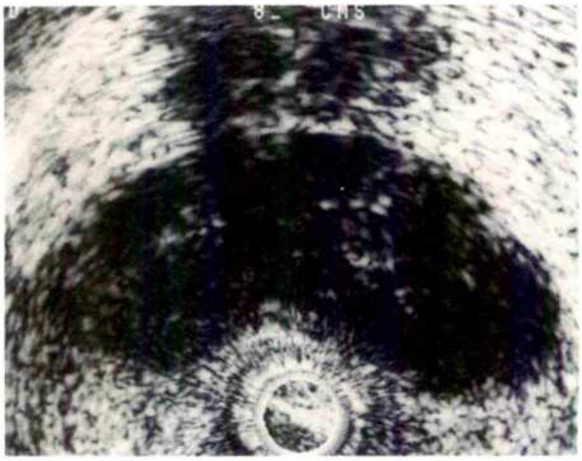

Fig. 4 T1 carcinoma of prostate occupying left lobe.

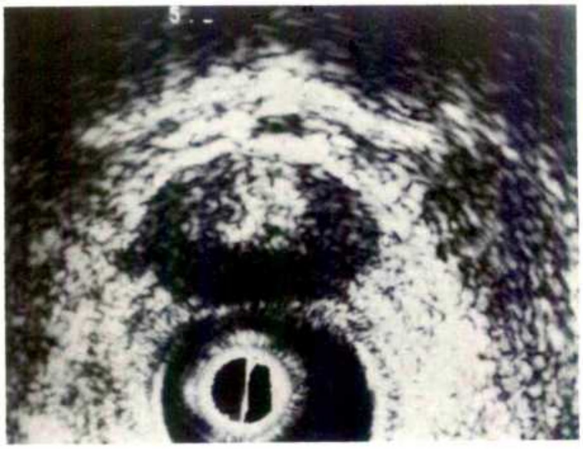

Fig. 5 Localised prostatic carcinoma: clinically T2.

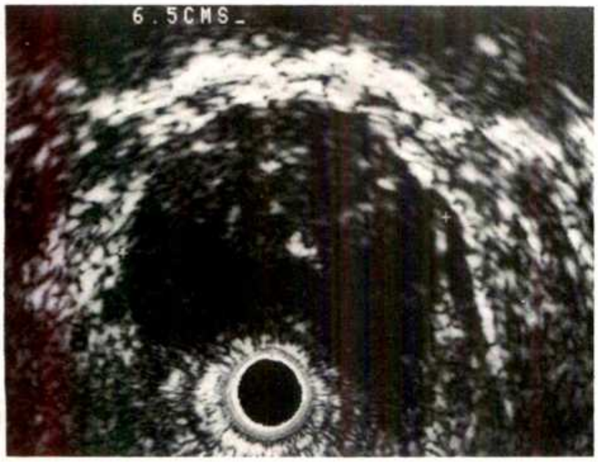

Fig. 6 T0 prostatic carcinoma proven histologically. Ultrasonic appearances suggest benign hyperplasia.

the use of multiple, ultrasonically guided biopsies of suspicious areas may be particularly rewarding.

In common with most workers, we are satisfied that prostatic ultrasound is an accurate method for diagnosing BPH and assessing gland volume. Indeed, in some centres the technique is used routinely to assess the size of gland pre-operatively, thereby allowing the surgeon to plan his operative approach well in advance (Miyazaki *et al.*, 1983).

We agree that the technique is an excellent one for staging proven prostatic cancer, but we have reservations as to its accuracy in diagnosing early tumours in view of the reported false positive and negative rates (Okafor *et al.*, 1983). It may be argued that the false positives are an acceptable price to pay for detecting more early cancers but it remains to be seen whether earlier detection will result in improved survival. The high false negative rate is disappointing and future work should be aimed at reducing this. Technical advances, particularly in the tissue characterisation field, may make this goal easier to achieve. Until such time we would be loathe to recommend the technique as a mass screening procedure for cancer.

Our experience of the use of ultrasound in prostatitis is too limited to draw any conclusions. Peeling and Griffiths (1984) have recently reviewed its role in both diagnosis and assessment of treatment in this condition. They described the ultrasonic features of acute and chronic prostatitis and reiterated the difficulty in distinguishing the latter from prostatic cancer on ultrasonic findings alone. Factors such as the patient's age and clinical findings must be considered and a biopsy is often the final arbiter.

In addition to its diagnostic role, prostatic ultrasound may have a therapeutic function with the advent of ultrasonically guided precise needle placement in the prostate, which allows percutaneous implantation of radioisotopes into the gland for the treatment of localised cancer (Holm *et al.*, 1983).

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The Authors

C. Kadow, FRCS, Research Registrar, Department of Urology.
J. C. Gingell, FRCS, Consultant Urologist.
J. B. Penry, FFR, DMRD, Consultant Radiologist.

Requests for reprints to: C. Kadow, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

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Long-term Follow-up after Transurethral Prostatic Resection With or Without a Short Peri-operative Antibiotic Course

M. GRABE and S. HELLSTEN

Department of Urology, University of Lund, Malmö General Hospital, Malmö, Sweden

Summary—This study was undertaken to analyse the results in 192 patients who 3 to 4 years earlier had undergone transurethral resection (TUR) in a controlled clinical trial on the value of a short peri-operative course of antibiotics. The survival rate was comparable in both groups. Most deaths were due to cardiovascular disease and/or cancer of the prostate and the gastrointestinal tract. Infectious events predominated in the control group and more antibiotics were prescribed for these patients during follow-up than for the patients in the peri-operative antibiotic group. Bacteriuria was found in 24% of patients, evenly distributed between the groups. Eighty-three per cent were satisfied with the results of prostatectomy but 38% complained of symptoms from the lower urinary tract. The maximum urinary flow rate was not influenced by the presence of bacteriuria and/or symptoms. There was no difference between the groups regarding mortality or morbidity except for the frequency of post-operative urethral stricture formation, which was significantly higher in the controls. It was concluded that prospective long-term follow-up is indicated to assess the effect of short peri-operative antibiotic courses.

Transurethral resection has replaced open surgery in most cases of obstruction due to prostatic enlargement. The advantages are decreased mortality and morbidity, less discomfort for the patients and shorter hospitalisation. Earlier reports have focused on post-operative mortality and morbidity and long-term complications such as incontinence, epididymitis and urethral stricture (Davis, 1931; Holtgrewe and Valk, 1964; Bandhauer and Madersbacher, 1969; Singh *et al.*, 1973; Melchior *et al.*, 1974; Lund and Dingsør, 1976; Obrant, 1976; Chilton *et al.*, 1978). The present study was undertaken to review the outcome in 192 patients who underwent TUR and were enrolled in a controlled clinical trial that had started 4 years earlier. The aim of the initial trial was to evaluate the effects of a short antibiotic course on early post-operative infectious complications and bacteriuria. These were found to be significantly reduced when compared with an untreated control group. The clinical results have been presented in a previous report (Grabe *et al.*, 1984a), as have been the bacteriological findings (Grabe *et al.*, 1984b). The aim of the present study was to determine retrospectively whether a short peri-operative antibiotic course had any impact on long-term mortality and morbidity, with particular emphasis on survival rates, infectious episodes and related long-term complications and the patients' appraisal of the results of operation.

Patients and Methods

For 1 year, starting on 15 March 1978, 192 patients who were to undergo transurethral prostatic resection were enrolled in a prospective trial. As already described (Grabe *et al.*, 1984a), 98 patients were randomly assigned to a short peri-operative course of cefotaxime while 94 patients served as controls without antibiotic therapy. The mean age of the

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Table 1 Number and Cause of Death in 192 Patients. Mean Follow-up 3.5 Years

			Cause of death			
Time of death	*No. of deaths*	*Alive (%)*	*Cardiovascular disease*	*Cancer of prostate*	*Other cancer*	*Respiratory or renal disease*
<1 month	3	98.4	2*	—	1	—
1 month-1 year	7	94.8	4	2	1	—
1-2 years	8	90.6	3	4	1	—
2-3 years	17	81.8	5	5	3	4
3-4 years	6	78.6	4	—	2	—
Total	41	78.6	18	11	8	4

* One case of acute heart failure and one of septicaemia, severe bleeding and cardiac failure.

patients at the time of operation was 71 years. The two groups were comparable in terms of age, pre-operative catheter treatment and prevalence of bacteriuria, operative procedure and post-operative care, concomitant disease and weight of and malignancy in the resected specimen. Four years later all case records were reviewed and the patients were asked to complete a questionnaire. A urine sample for culture was collected and uroflowmetry undertaken in most cases. The primary cause of death as indicated in the autopsy records (26) and death certificates (15) was examined in the patients who had died during the observation period. Four years after the start of the trial 41 patients had died. Of the 151 patients alive 19 could not participate because they were seriously ill (3), had moved to another town (4) or could not be reached (12). A questionnaire was sent to the remaining 132 patients, 110 of whom answered most of the questions. Twenty-two patients did not co-operate either because of serious disease (8) or they refused even after personal contact (14).

The questionnaire The patients were asked:

(i) if their voiding after the operation was (a) much improved, (b) improved, (c) unchanged, (d) worse.
(ii) if they had any remaining symptoms from the lower urinary tract such as (a) pain when passing urine, (b) frequency, (c) terminal dribbling, (d) poor stream, (e) turbid and/or foul-smelling urine.
(iii) about the frequency of nocturnal voiding before and after TUR.
(iv) if they had been prescribed any antibiotics during the observation period.

Uroflowmetry All patients answering the questionnaire were asked to carry out uroflowmetry with a DISA mictiograph (21F05). The maximum flow rate and voided volume were considered.

Urine culture Cultures were run with routine quantitative assays and the sensitivity of the bacteria was assessed with a disc diffusion method (Grabe *et al.*, 1984b).

Definitions All diagnoses were made on a clinical basis. Septicaemia was defined as a positive blood culture with high fever and systemic symptoms. Upper urinary tract infection (UTI) was diagnosed as fever associated with flank pain and/or systemic symptoms and positive urine culture. Lower UTI was defined as symptoms of cystitis with a positive urine culture. Chronic bacteriuria was recorded when it recurred despite several discrete antibiotic courses. Stricture of the meatus or other parts of the urethra and of the bladder neck was suspected when patients complained of a poor urinary stream with or without lower urinary tract symptoms. The diagnosis was made by a typical uroflowmetry curve and confirmed by inspection, urethrocystoscopy or urethrocystography. A stricture was defined as a narrowing of the urethra requiring surgical treatment.

Results

Mortality Forty-one patients (21%) died during the follow-up period. The primary causes of death are listed in Table 1. Three patients died within the first month, one from septicaemia. This patient, who belonged to the control group, was the only fatality directly attributable to an infectious complication following TUR. Acute and chronic cardiovascular disease (including pulmonary embolism) caused most deaths (18), followed by metastatic prostatic cancer (11) and other cancers (8), mainly gastrointestinal. In most patients a combination of cardiovascular and malignant disease was observed. The mean age of these patients at the time of death was 75 years. Twenty patients

Table 2 Infectious Events and Stricture of the Urethra Observed Between 6 Weeks and 3 Months and More Than 3 Months after TUR in 192 Patients (98 in Cefotaxime Group and 94 in Control Group)

	6 weeks-3 months		*After 3 months*	
Diagnosis	*Cefotaxime group*	*Control group*	*Cefotaxime group*	*Control group*
Infections				
Septicaemia	—	—	1	1
Upper UTI	—	—	1	3
Lower UTI	6	13	7	12
Epididymitis	1	—	—	1
Chronic bacteriuria	—	—	4	7
Stricture				
Meatus	—	—	1	3
Urethra (other parts)	—	—	—	4
Bladder neck	—	—	1	3

belonged to the cefotaxime group and 21 to the control group.

Morbidity The complications occurring up to 6 weeks post-operatively have been reported by Grabe *et al.* (1984a). Table 2 shows the late infectious episodes and complications. There was a predominance of infection in the control group. Septicaemia occurred in two patients, in one due to calculus pyelonephritis and in the other after instrumentation for stricture of the urethra, the latter patient not being covered by an antibiotic. Upper urinary tract infection was recorded in four patients and could be related to predisposing factors such as pelvic stones in two cases and recurrent UTI in one diabetic patient. The fourth case followed a revision TUR due to obstruction from residual prostatic tissue. The number of lower urinary tract infections was higher in the control group (25) than in the cefotaxime group (13). This was also the case for chronic recurrent bacteriuria, diagnosed in seven cases in the former and four in the latter group. Antibiotics were prescribed for more patients in the control group (25) than in the cefotaxime group (18) during the whole period as recorded in the case notes and the questionnaires.

Bacteriuria At the follow-up examination, bacteriuria was noted in 24/100 patients, 14 in the cefotaxime group and 10 in the controls. Five of these had significant bacteriuria ($>10^8$ cfu/l) and 19 non-significant (10^7-10^8 cfu/l). The Gram-negative species predominated (27/29 isolated strains). The proportion of patients with pre-operative indwelling catheters (37%), bacteriuria (46%) or carcinoma of the prostate (21%) did not differ markedly from the rates in all patients. No overrepresentation of predisposing factors such as urinary tract stone (1) or bladder cancer (2) was found in these patients.

Stricture of the urethra or bladder neck Post-operative stricture of the urethra or bladder neck was observed in 12 patients (Table 2), 2 in the cefotaxime group and 10 in the control group ($P=0.03$). Four of the strictures were a soft narrowing of the external meatus, two of which had been noted before TUR and treated by simple repeated dilatation. Even after exclusion of the four meatal strictures, a barely significant intergroup difference was recorded ($P=0.05$). Of the four patients with stricture of other parts of the urethra one received a permanent perineal urethrostomy and one was treated by dilatation. Two patients refused surgical treatment and continued to have a poor stream. Three of the bladder neck obstructions were treated by bladder neck reconstruction and one by transurethral bladder neck incision. The clinical features in the stricture patients are compared with those in all patients in Table 3. Three of 12 patients (25%) with stricture had bacteriuria in the late follow-up urine culture, *i.e.* the same proportion as in the series as a whole.

Instrumentation and operations Four patients in each group underwent a second TUR for benign or malignant residual glandular tissue. Sixteen patients, evenly distributed between the two groups, were subjected to urethrocystoscopy once or several times for assessment of bladder cancer or other endoscopic diagnosis (Table 4).

Patients' appraisal The patients' opinions on the results of prostatectomy 3 to 4 years after TUR were similar in both groups (Table 5). Eighty-eight patients (83%) were satisfied with the result of the

Table 3 Clinical Features in 12 Patients with Stricture of the Urethra Compared with all Patients

Clinical features	*Patients with stricture (n = 12)*	*All patients (n = 192)*
Age, years (mean)	66.0	71.3
% with indwelling catheter before TUR	33	37
% with pre-operative bacteriuria	41	42
% with post-operative bacteriuria	58	16-54*
% with prostatic cancer	25	24
Weight of the resected specimen (g, mean)	7.0	15.8
Hospitalisation, days (mean)	9.4	7.4

* In cefotaxime and control groups respectively, 10 days after TUR.

Table 4 Instrumentation and Endoscopic Operation in 192 Patients after TUR. Mean Follow-up 3.5 years

Instrumentation/operation	*Cefotaxime group*	*Control group*
Cystoscopy	9	7
Revision TUR/bladder neck incision	5	4
Open bladder neck reconstruction	0	3
Lithotripsy	1	0

Table 5 106 Patients' Appraisal of TUR. Mean Follow-up 3.5 years

	Cefotaxime group	*Control group*	*Total*	*Percentage*
Much improved	32	20	52	49
Improved	15	21	36	34
No change	4	7	11	10
Worse	4	3	7	7

operation. Sixty-three (59%) had no remaining symptoms, whereas 40 (38%) complained of one or more symptoms related to the lower urinary tract (Table 6). Bacteriuria was found in the same proportion of patients with symptoms (24%) as without (25%). Twenty of 24 bacteriuric patients (83%) were satisfied with the operation. Three complained of incontinence. The frequency of nocturnal voiding before and after operation is illustrated in Figure 1. A significant reduction was demonstrated post-operatively ($P < 0.01$).

Uroflowmetry Ninety-three patients carried out uroflowmetry with a voided urine volume of ⩾100 ml, 67 with a volume ⩾150 ml. The mean maximum flow rate was 14.5 ml/s (range 2-25) and the distribution is shown in Figure 2. Thirty patients had a maximum flow exceeding 15 ml/s. The flow rate for patients complaining of lower urinary tract symptoms was 13.3 ml/s compared with 15.4 in patients without symptoms. Bac-

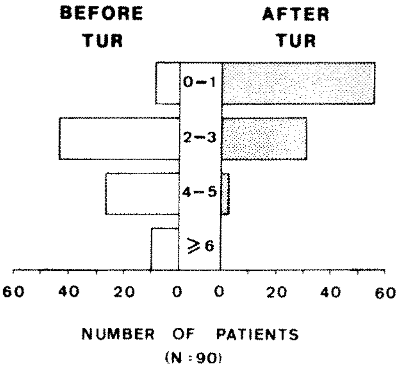

Fig. 1 Frequency of nocturnal voiding in 90 patients before and 3 to 4 years after TUR. Figures in the central area express the frequency of micturition.

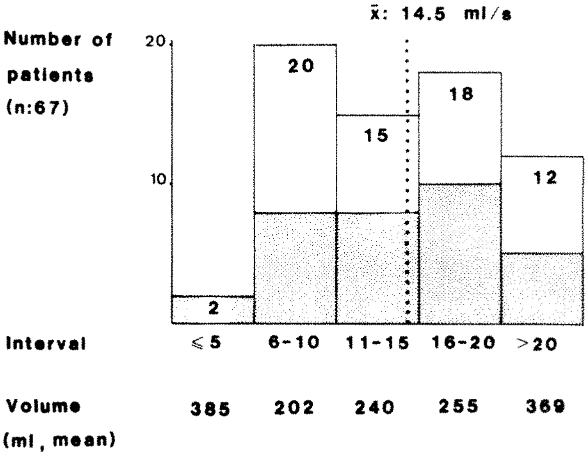

Fig. 2 Distribution of maximum flow rates obtained 3 to 4 years after TUR from 67 patients (voided volume ⩾150 ml), 33 from the control group (dotted area) and 34 from the cefotaxime group (white area). Figures within the bars represent the total number of patients for each flow rate interval. The lowest row indicates the mean voided volume for the patients in each interval. The mean maximum flow rate for all patients was 14.5 ml/s.

Table 6 Remaining Symptoms in 106 Patients. Mean Follow-up 3.5 Years

Symptoms	*Cefotaxime group* (*n* = 56)	*Control group* (*n* = 50)	*Total* (*n* = 106)	*Percentage*
No symptoms	37	26	63	59
Symptoms*	16	24	40	38
painful voiding	2	5	7	
frequency	4	11	15	
terminal dribbling	7	7	14	
poor stream	8	10	18	
turbid or foul-smelling urine	5	7	12	
Uninterpretable answer	3	—	3	3

* More than one symptom in some patients.

teriuric patients had a mean maximum flow of 14.0 ml/s. Distribution between the groups was symmetrical and no statistical difference was found.

Discussion

In a previous study we demonstrated the efficacy of a short peri-operative antimicrobial course with cefotaxime to reduce the frequency of infectious complications and bacteriuria in patients undergoing TUR (Grabe *et al.*, 1984a). In this retrospective review we have analysed the results over an average period of 3.5 years after TUR in an attempt to assess the effect of the antibiotic course on late mortality and morbidity, whether these were due to infection or not. Late mortality during the follow-up period could be ascribed to either cardiovascular or malignant disease, mainly cancer of the prostate and the gastrointestinal tract. No difference between the groups was found. Although no fatal infectious episodes arose during the period of observation, there were two severe infectious complications following endoscopic procedures in patients without appropriate antibiotic cover. These events underline the value of an adequate course of antibiotics in conjunction with such urological procedures at least in bacteriuric patients undergoing TUR (Williams *et al.*, 1980; Hargreave *et al.*, 1982; Olsen *et al.*, 1983; Grabe *et al.*, 1984a) or other urological instrumentation procedures (Korbel and Maher, 1976).

Late infectious episodes predominated in patients in the control group compared with those who had received cefotaxime peri-operatively at TUR. Many patients in the control group were also prescribed antibacterial agents. Bacteriuria was found in 24% of patients at late follow-up after TUR but no causal factor could be defined. It is known that the prevalence of bacteriuria increases with age and may be explained by changes in bladder function, size of the prostate gland, immunological status and concomitant disease (Freedman, 1983). This is particularly true for elderly institutionalised men (Nicolle *et al.*, 1983). Our study, concerned with men who had undergone prostatectomy, confirms the high prevalence of bacteriuria in the elderly (mean age 75 years) despite elimination of prostatic obstruction. A peri-operative antibiotic course did not influence the long-term outcome regarding bacteriuria.

Most patients (83%), bacteriuric or not, were satisfied with the outcome of the operation and other workers have reported similar findings (Singh *et al.*, 1973; Lund and Dingsør, 1976; Chilton *et al.*, 1978). Nevertheless, 39% reported one or more symptoms related to the lower urinary tract regardless of the presence of bacteriuria. Neither lower urinary tract symptoms nor the presence of bacteriuria could be related to a significantly reduced maximum urinary flow rate.

Urethral stricture formation was found post-operatively in 12 patients. All strictures were attributed to TUR except for two meatal ones that were known prior to TUR. Ten strictures were observed in the control patients and only two in the cefotaxime group ($P < 0.05$). Treatment ranging from simple dilatation to open bladder neck reconstruction was required in 10 patients. Many reasons for post-operative stricture formation have been discussed, such as insufficient pre-operative calibration of the urethra, instruments that were too large, lengthy resections and urinary tract infections (Holtgrewe *et al.*, 1964; Madersbacher and Marberger, 1971; Lentz *et al.*, 1977). Low weight of the resected prostatic specimen has been reported to be a common feature in bladder neck stricture (Robinson and Greene, 1962; Holtgrewe *et al.*, 1964) and this was the case in our study. The patients with stricture formation followed the same pattern concerning the frequency of pre- and post-operative bacteriuria as those in the control group. However, our limited study does not allow us to identify bacteriuria as a specific causal factor. This is consistent with the findings of Hart and Fowler (1981) who, in a prospective study, failed to show any increase in the frequency of urethral stricture in bacteriuric patients. Nevertheless, our findings of a difference between the antibiotic and the control group suggests a relationship between stricture formation and infection.

In the long-term follow-up of patients undergoing TUR we found no late mortality attributable to infection. However, increased morbidity in terms of infectious episodes was recorded in patients with no antibiotic cover during TUR as compared with those who received antibiotics peri-operatively. The frequency of post-operative urethral stricture formation was significantly higher in the control group. It is therefore concluded that prospective long-term follow-up is essential to assess the risk of infectious events and stricture formation in patients with or without antibiotic cover at the time of TUR.

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The Authors

M. Grabe, MD, Senior Registrar.
S. Hellsten, MD, Associate Professor.

Requests for reprints to: M. Grabe, Department of Urology, Malmö General Hospital, S-214 01 Malmö, Sweden.

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Hyponatraemia Following Transurethral Resection of the Prostate

J. C. RHYMER, T. J. BELL, K. C. PERRY and J. P. WARD

Department of Urology, District General Hospital, Eastbourne

Summary—In a prospective study of 100 patients undergoing transurethral resection, changes in serum sodium were estimated during the per-operative and post-operative periods. The weight of prostate resected and the volume of irrigant fluid used influenced the changes in serum sodium. In 93 patients these changes were not statistically significant. In only seven patients were significant falls in serum sodium recorded, in one case to a level of 103 mmol/l. All seven exhibited the clinical features of the transurethral syndrome and there was one post-operative death which we attributed to it. The TUR syndrome undoubtedly exists and its incidence in this series was 7%. Its pathogenesis and clinical management are discussed.

A complication of transurethral resection of the prostate (TUR) characterised by bradycardia, hypotension and a post-operative confusional state together with profound hyponatraemia is called the TUR syndrome. It has been reported by Charlton (1980), Reiz *et al.* (1981) and Bird *et al.* (1982) and can cause sudden death on the operating table or in the post-operative period (Osborn *et al.*, 1980). Massive absorption of irrigant fluid causing haemodilution has been postulated as the cause of this syndrome. Changes in serum sodium levels can be used as an index of the degree of dilution and a prospective study was undertaken to investigate these changes. The aim of the study was to recognise the syndrome and to establish its incidence in a general urology unit.

Patients and Methods

A prospective study was undertaken of 100 consecutive patients undergoing TUR between October 1983 and June 1984. Their ages ranged from 54 to 90 years with a mean of 72 (SD ± 7.17).

The procedures were carried out using Storz Iglesias continuous flow resectoscopes (25 or 28F) and the irrigant fluid was 1.5% glycine with a pressure head of approximately 1 m above the operating table. Throughout the procedure all patients received 1 l Hartmann's solution intravenously (IV) and 1 mg Burinex (bumetanide) IV at the end. Post-operatively, all patients received an IV infusion of Hartmann's solution alternating with 5% dextrose 1 litre 8-hourly. This was continued until each patient was drinking satisfactorily, usually on the first post-operative day.

Serum sodium and other electrolytes were measured immediately before and after resection prior to administration of the diuretic, and on the first post-operative day. The samples were analysed in a multichannel analyser with an error of ± 3 mmol serum sodium at a test level of 140 mmol. The volume of glycine used for irrigation and the weight of the prostate resected were recorded.

Within the group of 100 patients, due to slightly different operative techniques by the two consultant urologists, two subgroups were defined:

(i) Those using suction drainage of glycine with an apparatus giving a pressure of − 5 cm of water during resection. There was no post-operative irrigation in this group (49 patients).

(ii) Those using gravity drainage of glycine during resection but continuous bladder irrigation using glycine in the post-operative period (51 patients).

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Results

Most patients tolerated transurethral resection extremely well with minimal changes in the serum sodium levels. There was a mean fall of 3.65 mmol/l during the operation and a further fall of 1 mmol by the first post-operative day. These changes, however, were not statistically significant. The mean weight of prostate resected was 27 g and the mean volume of irrigant 15.25 l of glycine (Table 1).

Table 1 Changes in Serum Sodium Levels

	Overall	*Group A*	*Group B*
Number of patients	100	49	51
Age	72 (7.2)	71.4 (7.2)	72.6 (7.1)
Volume of glycine (l)	15.25 (6.58)	16.29 (6.98)	14.73 (6.03)
Weight of prostate (g)	27.5 (15.3)	27.9 (16.3)	27.0 (13.4)
Per-operative sodium fall (mmol/l)	3.65 (5.67)	3.71 (6.07)	3.59 (4.15)
Post-operative sodium fall (mmol/l)	0.96 (4.63)	1.06 (4.71)	0.18 (4.48)

All results are Mean ± SD

Seven patients (7%) developed significant post-operative hypotension with hyponatraemia (Table 2). The intra-operative fall in serum sodium in these cases was from 6 to as much as 32 mmol/l. In 100 patients there was a significant correlation between the weight of prostate resected and the per-operative sodium fall ($P<0.05$), but by the first post-operative day this was no longer the case because of the inverse correlation between weight of gland and post-operative sodium fall ($P>0.05$). There was a similar strong correlation (coefficient of correlation 0.76 ($P<0.05$) between the weight of gland resected and the volume of glycine used. Comparing the two subgroups A and B, there was no significant difference between them when considering any results.

Whilst the results showed an overall fall in serum sodium levels, there were two distinct trends. Patients with larger glands tended to show a greater per-operative sodium fall and a post-operative recovery of serum sodium levels. Hence in the 22 patients whose glands weighed 40 g or more, the mean per-operative fall was 6 ± 7 mmol/l compared with 3 ± 4.2 mmol/l in the remaining 78 patients ($P<0.05$); in the post-operative period a change of + 1.36 mmol ± 6.14 mmol/l occurred, compared with − 1.61 ± 4 mmol/l ($P>0.05$). Both groups attained similar levels on the first post-operative morning.

In none of the seven patients found to be hypotensive post-operatively could the effect of anaesthetic agents or blood loss be found to be contributory. Significant falls in serum sodium levels were recorded in all of these patients and are shown in Table 2. Of this group, cases 3 and 6 were operated upon for retention of urine and the others were elective procedures. Only in case 4 was the histology malignant. Case 5 was a 79-year-old gentleman who underwent a 56 g resection under general anaesthesia and post-operative catheter irrigation was not employed (*i.e.* Group A). He developed a profound TUR syndrome and although intravenous diuretics and calcium were employed he made little clinical recovery, although his plasma sodium rose from 103 to 120 mmol/l, and he died on the second post-operative day from left ventricular failure and huge bilateral pleural effusions. His dilutional picture was compounded by the effects of blood loss, and after biochemical correction had become apparent it was thought that his continuing hypotension could, in part, be due to blood loss. He was accordingly transfused 2 units of packed cells slowly and although he tolerated these at the time, he subsequently died. We believe

Table 2 Details of 7 Patients with Post-operative Hypotension and Hyponatraemia

				Serum sodium (mmol/l)		
Patient	*Age*	*Wt. of gland (g)*	*Volume of glycine (l)*	*Before resection*	*After resection*	*First day*
1	77	25	16	139	120	130
2	84	70	30	141	125	136
3	71	25	18	137	125	138
4	76	18	6	139	133	130
5*	79	56	45	135	103	120
6	81	20	18	137	129	133
7	71	15	12	136	111	125

* This patient died on the second-post operative day.

his death was attributable to altered capillary permeability and intercurrent cardiovascular disease. At post mortem cerebral oedema was not present.

Discussion

Osborn *et al.* (1980) reported three patients who collapsed after prostatectomy and were found to be profoundly hyponatraemic. In these cases there was the paradoxical combination of bradycardia and hypotension. Creevy (1947) attributed this so-called TUR syndrome to the use of water irrigation being infused intravenously via the prostatic venous plexus and so causing haemolysis, but the same has been reported with glycine and mannitol (Logie *et al.*, 1980). Oester and Madsen (1969), using radioisotopes, found the absorption of irrigating fluid could be up to 4 l of which the intravascular component could be up to 1.8 l.

The entering of periprostatic venous spaces during resection, permitting irrigant absorption and bladder overdistension, is a predisposing factor. Consideration has been given to preventing the syndrome by the reduction of irrigating pressure during resection. The Iglesias continuous flow resectoscope maintains an intravesical pressure of 10 mmHg and should in theory achieve this. Stephenson *et al.* (1980), however, found no significant difference in serum glycine (and serine, its metabolite) estimations when comparing intermittent and continuous flow and concluded that in both techniques similar volumes may be absorbed.

Treatment of the established case is controversial. Charlton (1980) recommended the administration of potent loop diuretics and hypertonic saline together with positive inotropes and calcium. By contrast, Bird *et al.* (1982) advised "masterly inactivity" by withdrawing all treatment and they felt that the use of hypertonic solutions was contraindicated for fear of precipitating pulmonary oedema. The policy of our unit was to administer 10 ml of 10% calcium gluconate (IV) and a further dose of diuretic, to restrict fluids and to await events. Six of the seven patients diagnosed as having the syndrome recovered within 48 h. In the post-operative phase, the trend was for sodium levels to increase in patients with larger glands and in whom there had been a large post-operative fall. Conversely, the trend was for sodium levels to decrease post-operatively in patients with small glands in whom there had been a small per-operative fall. Thus, when considering the overall change in serum sodium, we could find no statistical correlation with weight resected or with the volume of glycine used.

Comparison between the two subgroups A and B, which were statistically matched and yet were not chosen by a randomised controlled method, seems to suggest that neither suction drainage during resection nor post-operative irrigation affects the serum sodium changes.

We believe a per-operative fall in serum sodium of 15 mmol/l or more may lead to serious consequences if untreated, although lesser falls in serum sodium may occur in patients who exhibit the clinical features of the TUR syndrome. Careful diagnosis and treatment of the pulmonary complications is paramount and may possibly have prevented the one death in our series. Further studies are in progress.

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The Authors

J. C. Rhymer, MB, BS, Senior House Officer.
T. J. Bell, FRCS, Registrar.
K. C. Perry, FRCS, Consultant Urologist.
J. P. Ward, MS, FRCS, Consultant Urologist.

Requests for reprints to: J. P. Ward, Department of Urology, District General Hospital, Eastbourne, East Sussex BN21 2UD.

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Serial Prostatic Histology

A Valid Marker of Response to Hormone Treatment

M. C. BISHOP, I. D. ANSELL, M. C. TAYLOR and A. L. THOMAS

Departments of Urology and Histopathology, City Hospital, Nottingham; Department of Urology, District General Hospital, Rotherham

Summary—Serial transrectal needle biopsies were taken from 146 patients (657 specimens) with advanced prostatic cancer (T3/T4, M1/M0) admitted to a trial of two forms of oestrogen therapy. Histological grading by Gleason and Mostofi techniques on the initial biopsy showed no correlation either with extent of disease or its eventual outcome on treatment. Change in grade was dissociated from the response of bone metastases to hormone treatment and did not appear to influence survival. However, the prognosis of 16 patients showing clearance of tumour from their serial biopsies was generally good.

The treatment of patients with advanced prostatic cancer is palliative and therefore, for some urologists, observation of clinical progress is adequate for monitoring disease activity. However, closer objective control is required in investigative work, particularly in comparing treatment regimes. Serial quantitative bone imaging by isotope scintigraphy is generally accepted as the standard test of skeletal metastatic activity, although plasma alkaline phosphatase with isoenzyme analysis may be a cheaper and more sensitive alternative (Killian *et al.*, 1981; Pontes, 1983; Bishop *et al.*, 1985). Progress of local disease is more problematic. Serum prostatic acid phosphatase is said to reflect the extent of malignancy overall, but chemical enzyme estimation is acknowledged as relatively insensitive. The more recently described immunological methods may have some advantage in terms of improved sensitivity but are likely to lack selectivity as markers of tumour activity and again will not separate local from metastatic disease. Objective assessment of change in dimensions and consistency are now possible with developments in techniques of transrectal ultrasound but direct examination of prostatic tissue has to remain the "gold standard".

In Scandinavia and Germany, quantitative cytology of prostatic aspirate has been found highly satisfactory both for diagnosis of suspicious areas on rectal examination and in follow-up (Esposti, 1982). Elsewhere, where there may be less expertise in these techniques, histopathological examination of larger volumes of tissue is the method of choice (Murphy and Whitmore, 1979; Ansell, 1982) and many methods of semi-quantitative grading on an initial pre-treatment biopsy are said to correlate with the eventual outcome. However, doubts have been cast on the validity of these techniques (Byar and Mostofi, 1972; Kastendieck, 1980; Muller *et al.*, 1980). Comparison between histology of material taken from radical prostatectomy specimens and needle biopsy indicates that considerable heterogeneity may be underestimated in a small core of tissue. This problem is recognised but perhaps not fully accounted in Gleason's method of grading, where extremes of glandular differentiation are scored separately for each section (Gleason, 1966). Assessment of consistency of change in a serial study on specimens obtained at intervals during treatment will also reflect on the validity of needle biopsy as a measure of treatment response in the primary tumour. The results of several studies are available from patients treated with radical radiotherapy, but there is less information on serial histology from patients on primary hor-

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monal treatment. In the present study, the value of serial prostatic histology has been assessed in patients with advanced local disease on a trial of two forms of hormonal treatment.

Patients and Methods

One hundred and forty-six patients (mean age 72 years; range 56-87) were admitted to a randomised trial of diethylstilboestrol (3 mg/day) against estramustine (560 mg/day) as primary treatment for advanced prostatic cancer (T3/T4 disease, with or without bone metastases: M1 or M0). Serial transrectal needle biopsies (Trucut, Travenol Ltd) were taken.

Every specimen was examined independently by two histopathologists experienced in urological disease. Mostofi (1975) and Gleason (1966) gradings were used. For the latter, a composite figure (for best and least differentiated parts of the section) was obtained, giving a maximum total count of 10. Mostofi's system provides an assessment of both glandular and cytological differentiation. The possible maximum scores for each are 4 and 3 respectively. In the present report the total Mostofi scores are presented (maximum 7) (Table 1). For some of the analyses a single figures was obtained from the addition of Mostofi and Gleason gradings. In a few cases, where the prostatic origin of the cancer was in doubt, specific histochemical confirmation was sought by positive identification of prostate-specific antigen.

Table 1 Mostofi System of Grading—Numerical Equivalent

Anaplasia (nuclear)	
Slight	1
Moderate	2
Marked	3
Differentiation (glandular)	
Large	1
Small	2
Cribriform-fused	3
Columns and cords	4
Maximum total score	7

(Mostofi, 1975; Murphy and Whitmore, 1979)

Patients were investigated for bone metastases by serial quantitative skeletal imaging using ^{99m}Tc diphosphonate. Response of metastases to treatment was summarised for each patient into one of six groups on a basis of changes in bone scanning and plasma alkaline phosphatase (Table 2).

Table 2 Classification of Response of Bone Metastases to Hormonal Treatment as Expressed by:
(a) *Serial isotope imaging*

	Group 1	Normal imaging before and during treatment
	2	Normal imaging before treatment. Bone metastases developing on treatment
Positive imaging (bone metastases) pre-treatment	3	Imaging improving on treatment
	4	Imaging improving then deteriorating on treatment
	5	Imaging unchanged on treatment
	6	Imaging deteriorating on treatment

(b) *Serial plasma alkaline phosphatase (PAIP)*

	Group 1	Normal PAIP before and during treatment
	2	Normal PAIP before, rise during treatment
Elevated PAIP pre-treatment	3	Fall in PAIP on treatment
	4	Fall then rise in PAIP on treatment
	5	PAIP unchanged
	6	Rise in PAIP on treatment

(Bishop *et al.*, 1985)

Results

Six hundred and fifty-seven specimens were taken from 146 patients. In 12 patients only one (pretreatment) biopsy was studied. No follow-up specimens were available. In 134 patients, serial biopsy histology was evaluated with a mean period between initial and final biopsies of 24 months; 75 specimens were regarded as inadequate for evaluation of prostatic histology (11%).

Relevance of the Negative Biopsy

In 56 patients, serial biopsies showed no evidence of malignancy on at least one of the specimens, though often in these cases the appearance of ductal and acinar epithelium was modified by the presence of squamous metaplasia, indicating oestrogen effect. In only 16 patients from this group two or more biopsies, including the final one, showed no evidence of tumour. Clearance of tumour was inconsistent in the remaining 40 and followed by recurrence in subsequent biopsy material. In this context it should be emphasised that even in a single needle biopsy core considerable heterogeneity of tumour grading could occasionally be observed.

Table 3 Outlook for Patients Becoming Tumour-free on Serial Prostatic Biopsy

		Response of bone metastases to treatment			
		Groups 1–6			
Name	*Initial grade of primary tumour Gleason: Mostofi*	*Isotope*	*Alkaline phosphatase*	*Survival (months)*	*Cause of death*
WJ	4:2	1	1	A 60	
TM	5:2	1	1	D 48	Cerebrovascular accident
RW	4:2	1	1	A 50	
TH	5:2	1	1	A 51	
WC	5:3	1	1	A 64	
RH	5:3	1	1	D 43	Ischaemic heart disease
IN	6:3	1	1	A 42	
FO	7:5	1	1	A 73	
AS	6:6	1	2	D 25	Metastases
MD	6:4	1	2	D 7	Probable metastases
LM	6:3	2	1	D 65	Myocardial infarct
TR	8:5	2	1	A 45	
HS	5:3	2	4	A 66	
IR	8:5	3	1	A 44	
SM	6:3	3	3	A 23	
SW	9:4	4	4	D 24	Metastases

Classification of bone metastases as in Table 2. D = dead. A = alive.

Table 4 Response of Bone Metastases to Hormone Treatment in Relation to Initial Prostate Tumour Grade

Bone group	1	2	3	4	5	6
No.	56	13	16	9	13	12
Gleason mean	6.9	7.3	8.1	8.0	6.9	7.5
SD	1.4	1.3	1.2	1.5	0.9	1.3
Mostofi mean	4.7	5.3	5.6	5.3	4.8	5.4
SD	1.5	1.4	1.1	1.4	0.7	1.4

In general, clearance of tumour occurred in patients whose disease activity remained controlled on hormonal therapy for long periods. However, there were exceptions (Table 3).

Initial (Pre-Treatment) Histology—Relationship with Treatment Response

One hundred and nineteen patients were adequately documented by serial prostatic histology and skeletal imaging (Table 4). In 47%, serial bone scanning showed no evidence of metastases. The mean histological grading was not significantly different for groups with and without bone metastases. There was also no significant difference in mean initial grading between patients developing metastases (Group 2) and those in whom they pre-existed (Groups 3–6). However, survival of patients with and without metastases was compared. Each group was subdivided further into those whose initial biopsies gave a composite figure for the addition of Gleason and Mostofi gradings of more than 13 (poorly differentiated) and less than 13 (moderately differentiated). There was no significant difference between survival curves of patients classified according to histological differentiation. On the other hand, the difference between survival curves of M1 and M0 groups was highly significant (Fig. 1).

Relationship Between Progression of Primary Tumour and Bone Metastases

Fifty-three patients with bone metastases (positive isotope imaging) were evaluated (Table 5). In 28 patients the grade of the tumour in the prostate increased unequivocally. However, in 12 patients serial bone imaging suggested either improvement or that the metastatic disease was stable. Of 25 patients whose biopsies became downgraded or

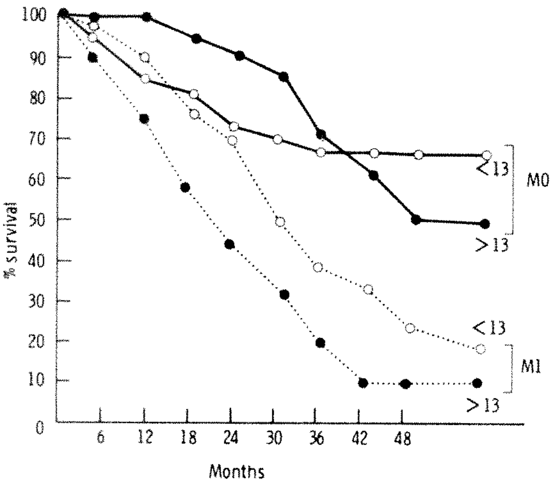

Fig. 1 Life table analysis of survival in groups with and without bone metastases (M1, M0) and initial grading of primary tumour scored > 13 (sum of Gleason and Mostofi) and < 13.

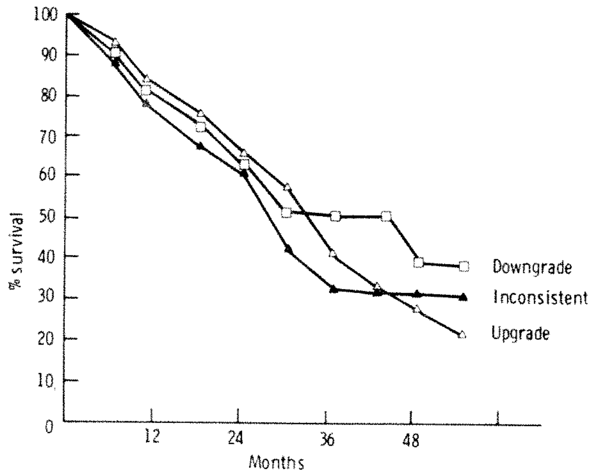

Fig. 2 Life table analysis of survival in groups defined by change in grade of primary tumour on hormone treatment.

were unchanged, 10 showed deterioration on serial bone imaging. The correlation was more significant when progress of bone metastases was regarded in terms of serial plasma alkaline phosphatase but only for the group whose prostate histology became upgraded ($P = 0.0006$).

Table 5 Relationship Between Treatment Response of Primary Prostatic Tumour and its Bone Metastases

		Scan	*Alkaline phosphatase*
Upgrade (n = 28)		28	36
Bone metastases↑	(2,4,6)	16	26
↓→	(3,5)	12	10
Downgrade/unchanged (n = 25)		25	30
Bone metastases↑	(2.4.6)	10	20
↓→	(3,5)	15	10

Primary tumour: upgraded = becoming less differentiated.
Bone metastases: Groups 2,4,6: progress adverse. Groups 3,5: progress favourable or unchanged (see Table 1).

Survival in Comparison with Change in Primary Tumour Grading

There was no significant difference between survival curves of groups defined by the direction of change in tumour grade (Fig. 2).

Discussion

Serial histology was evaluated as an index of local response by the prostatic tumour to primary hormonal treatment. Survival was influenced much more by the presence of metastases than initial tumour grade. It is acknowledged that patients were selected for advanced disease (T3/T4). Since stage and grade are closely correlated, very few patients with lower grade malignancy could have been included and consequently its expected beneficial effect on survival was lost. However, it is also possible that much of the previous data, relating survival to grading, reflected more on the influence of staging.

It was hoped that clearance of tumour, or at least reduction in histological grading, would correspond to diminished activity of bone metastases and that serial prostatic histology and bone isotope imaging supplemented with plasma alkaline phosphatase would give a consistent overall objective assessment of treatment response. However, there was considerable disparity between changes in activity of local and metastatic disease. To some extent this might have been due to the heterogeneity of tumour differentiation in the malignant prostate alluded to earlier. However, there are many examples in oncology of the dissociation between behaviour of primary and secondary tumours. The implication of persistence of tumour in the prostate after treatment is controversial. It is even uncertain whether cellular viability can be assumed from a static histopathological preparation. Nevertheless, the persistence or reappearance of tumour after radical radiotherapy to the prostate does at any rate seem to have sinister implications for ultimate metastatic spread (Kiesling *et al.*, 1980). There is less evidence available of serial prostatic histology from patients on hormone treatment. It has been stated that only 50% of patients with poorly differentiated tumours respond locally (Dhom and Hohbach, 1982). Hormone suppression of metastases is achieved more often. In the present series a biochemical and clinical response was obtained in 75% of patients, although the majority with bone metastases eventually relapsed. However, lack of "definitive conversion" (Jacobi, 1982) within the prostate did not necessarily imply a poor outlook, particularly in patients without metastases. Similarly, change in the grades, for better or worse, did not seem to influence prognosis. Therefore, the possibility that high grade malignancy treated hormonally could lie dormant within the prostate for several years should be reconsidered.

It is concluded that serial prostatic histology is unhelpful in forecasting overall disease activity since it bears no relationship either to progression of metastatic disease or to survival and is an unreliable measure of response to treatment, at least in the context of advanced local disease on hormone therapy.

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The Authors

M. C. Bishop, MD, MRCP, FRCS, Consultant Urologist, Nottingham City Hospital.

I. D. Ansell, MRCPath, Consultant Histopathologist, Nottingham City Hospital.

M. C. Taylor, FRCS, Consultant Urologist, Rotherham District General Hospital.

A. L. Thomas, MRCPath, Lecturer, Department of Histopathology, Nottingham City Hospital.

Reqeusts for reprints to: M. C. Bishop, Department of Urology, City Hospital, Hucknall Road, Nottingham NG5 1PB.

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Surgical Correction of Post-Operative Retrograde Ejaculation

A. E.-S. RAMADAN, M. I. M. EL-DEMIRY and A. E.-D. A. E.-S. RAMADAN

Departments of Urology, Om El-Masreyin and Police Authority Hospitals, Cairo, Egypt

Summary—Retrograde ejaculation is a known complication of bladder neck surgery. Revision of a bilharzial bladder neck obstruction accentuates the incidence of this complication. Some of the difficulties in the surgical correction of retrograde ejaculation are directly related to pathological changes caused by bilharziasis.

In this study a new length of premontanal urethra is formed using the trigonal urothelium and the trigonal muscles with their intact sympathetic innvervation to correct retrograde ejaculation following bladder neck surgery. Normal (antegrade) ejaculation was restored in four of five men using this procedure. The physiological basis of the procedure is discussed.

Surgery of the bladder neck and prostate is the commonest cause of retrograde ejaculation (Collins, 1982). This iatrogenic complication is of particular importance in Egypt, where the urologist is occasionally challenged by a case of retrograde ejaculation following surgery for bilharzial bladder neck obstruction.

In the present study the technique of intravesical tubulisation of the urethra (originally described by Dees (1949) for the treatment of urinary incontinence associated with congenital epispadias) was used in order to treat retrograde ejaculation following bladder neck surgery.

Patients and Method

During an 18-month period (June 1982–December 1983) five men (aged 22–37 years) presented with retrograde ejaculation following bladder neck surgery for the treatment of bilharzial bladder neck obstruction.

The procedure was wedge resection of the posterior lip of the internal urinary meatus in three cases and was undefined in two. Surgery of the bladder neck had been performed 6 to 40 months before presentation. In all five men retrograde ejaculation was noted immediately after the original surgery. There was increased frequency of micturition in two patients. Physical examination, neurological evaluation and laboratory and radiological findings were unremarkable in all patients. The presence of dye in the posterior urethra in a resting cystogram was observed in one patient only. Cystourethroscopy revealed a wide open internal urinary meatus in all cases.

Retrograde ejaculation was diagnosed by the patient reporting the feeling of ejaculation at orgasm but failing to find ejaculate coming from the external urinary meatus, together with retrieval of sperms from post-coital urine.

The technique used for the correction of retrograde ejaculation was the same in all cases (Fig.) The urinary bladder was opened through a vertical midline incision extending through the vesical neck along the roof of the prostatic urethra. A urothelial tube 1.5 cm in circumference was formed in the midline posteriorly from the urothelium of the trigone, around a 12 F catheter. This tube started a safe distance below the level of the ureteric orifices and extended caudally to the posterior lip of the internal urinary meatus or even into the prostatic urethra. The muscles of the bladder neck region on either side of the newly formed urethelial tube were

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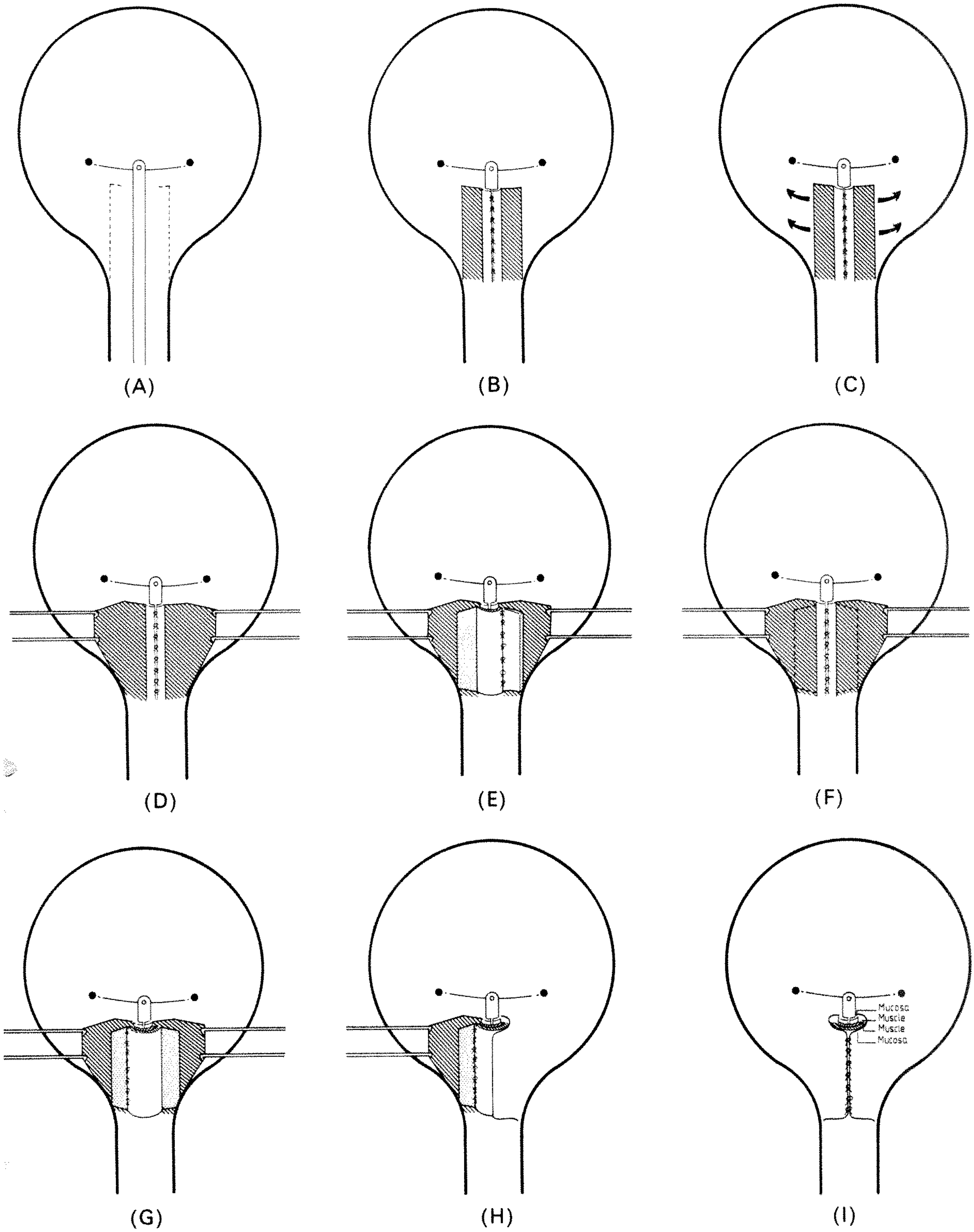

Fig. (A) Incisions are made to create flaps of mucosa large enough to wrap around a 12 F catheter. The size can be judged from a template of suture packet material. (B) The flaps are sutured around the catheter. (C) The mucosa is undermined laterally and can then be retracted. (D) An area of detrusor muscle is thus exposed. (E) Incisions are made to create two muscle flaps. The base of each is towards the midline. (F) The muscle flaps are "double breasted" around the new urethra. (G) The distal edge of each flap is sutured near the base of the contralateral flap. (H) The mucosal retraction is released. (I) The mucosal edges can be apposed at the midline.

denuded of urothelium and two lateral muscular flaps thus developed. By excising a rectangular piece from each flap they were fashioned so that one flap could be closely wrapped around the urothelial tube and sutured to the base of the contralateral flap. The second flap was wrapped around the first and sutured to its outer aspect. The urethral catherer was removed and the bladder closed around a suprapubic catheter which remained indwelling for 4 weeks. The cave of Retzius was drained for 10 days.

Results

In four patients the post-operative period was uneventful and convalescence was smooth. Normal ejaculation was regained immediately. Post-operative urographic studies revealed no significant residual urine and reflux was absent. Resting excretory cystograms demonstrated bladder base elevation.

The fifth patient suffered a stormy convalescence with bouts of high fever and bilateral loin pains. Retrograde ejaculation has persisted to the time of this report, 4 months post-operatively.

Discussion

Retrograde ejaculation is a known complication of bladder neck surgery and often follows open prostatectomy (O'Conor, 1979). It complicates 40% of transurethral prostatectomies (Reiser, 1961). Ochsner *et al.* (1970) reported a 33% incidence of retrograde ejaculation in men who had undergone open surgery of the bladder neck during childhood. Surgery for bilharzial bladder neck obstruction adds to the incidence of iatrogenic retrograde ejaculation in Egypt and is of particular significance in young patients, to whom fertility is extremely important.

Abrahams *et al.* (1975) were the first to report on the surgical correction of retrograde ejaculation following bladder neck surgery. Their study included two men in whom Y-V plasty had been performed. The procedure involved a transvesical approach to reconstruct the internal sphincteric mechanism. The muscles of the anterior two-thirds of the internal urinary meatus and proximal 1 cm of the urethra were bared by excising the overlying urothelium and fibrous tissue. The two sides of the bared muscles were sutured together by 3 to 4 sutures of zero chromic catgut in front of a 16 F catheter. The bladder was closed and the catheter left indwelling for 3 weeks. Both patients regained normal ejaculations and one of them has fathered a child. According to Collins (1982), Waterhouse (1979) had 6 successes out of 7 operations in which Abrahams' technique was used for patients with retrograde ejaculation following Y-V plasty during childhood.

We failed to restore normal ejaculation in two men treated by the Abrahams' procedure despite meticulous adherence to the technique. This suggested two possibilities. The first is that Abrahams corrects the disruption of the anterior segment of the internal sphincteric mechanism that has been sustained by the Y-V plasty. In wedge resection of the posterior lip of the internal urinary meatus the internal sphincteric mechanism is broken posteriorly and not anteriorly. Secondly, in patients who develop bilharzial bladder neck obstruction there is extensive circumferential fibrosis of the internal urinary meatus and proximal urethra, and this hampers the muscular action of these structures. Other healthy muscles have to be used to prevent retrograde ejaculation. These two possibilities provided the impetus for a search for a more suitable procedure for the correction of retrograde ejaculation in bilharzial patients, particularly those in whom the primary operation was not a Y-V plasty.

Normal antegrade ejaculation depends upon the co-ordinated powerful contraction of the internal urinary meatus and the premontanal urethra during or immediately after emission of semen into the urethra (Semens and Langworthy, 1938; Essenhigh *et al.*, 1969). For the contraction of these structures to be effective in preventing retrograde ejaculation the muscles must be healthy (not fibrosed), the lumen must not be abnormally wide and the premontanal urethra must be sufficiently long to exert an effective closure pressure. The contractions must be initiated and co-ordinated with the emission through normal sympathetic innervation (Kleeman, 1970).

An operation for the correction of retrograde ejaculation must restore all of the above normal conditions and the Dees (1949) procedure appeared to comply with this requirement. A long premontanal urethra with a non-dilated lumen is fashioned and is coated by the sympathetically innervated trigonal muscle which is fortified by detrusor flaps.

Our results have justified the choice of this procedure. Failure to restore normal ejaculation in one patient may have been due to post-operative infection disrupting the newly formed tube.

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The Authors

A.E.-S. Ramadan, MB, BCh, DS, DU, MCH, FICS, Consultant Urologist, Om El-Masreyin and Police Authority Hospitals.

M. I. M. El-Demiry, MB, BCh, MSc(Urol), formerly Urologist, Police Authority Hospital. Now Post-graduate Student, University Department of Surgery/Urology, Western General Hospital, Edinburgh.

A. E.-D. A. E.-S. Ramadan, MB, BCh, Registrar in Urology, Om El-Masreyin Hospital.

Requests for reprints to: M. I. M. El-Demiry, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Direct Vision Internal Urethrotomy in the Treatment of Urethral Fistulas due to Urethral Strictures

S. B. SHAH and V. G. MEHENDALE

Department of Surgery, Seth V.C. Gandhi and M.A. Vora Municipal General Hospital, Bombay, India

Summary—Five cases of urethral fistula—three with single and two with multiple fistulous tracts—were treated by optical urethrotomy. All of the fistulas healed completely.

Urethral fistula is a common complication of urethral stricture in India. There may be a fistulous tract with a single external and internal opening or the stricture may be complicated by multiple urethral fistulas presenting as a "watering-can perineum". Urethral fistulas can cause severe morbidity as a result of recurrent infection, abscess formation and dribbling of urine from the perineal openings during micturition.

Patients and Methods

Five patients with urethral fistulas due to urethral strictures have been treated over the last 5 years (Table). Two patients had multiple fistulous openings in the perineoscrotal region and three had a single fistulous opening in the perineum. All had urinary infections. In each case ascending and in some cases descending urethrograms were obtained (Fig. 1). All patients had strictures distal to the internal openings of the fistulas. Suprapubic cystoscopy was done in a patient who had a suprapubic puncture cystostomy.

In two patients who presented with periurethral abscesses the abscesses were drained and appropriate antibiotics given. Both developed a single urethral fistula following drainage of the abscess (Fig. 2). One patient had a severely thickened and acutely inflamed scrotal wall with multiple abscesses and openings over the scrotum, perineum and ischial tuberosities, all discharging pus and urine. The abscesses were drained and the wound allowed to granulate.

In all cases the stricture was divided by the optical urethrotome and an 18 or 20F Foley catheter left *in situ* for 7 to 10 days. Antibiotics were given to all patients until the urine was sterile.

Results

After removal of the catheter all patients had a good urinary stream, with minimal leakage from the fistulous openings for a few days. In three

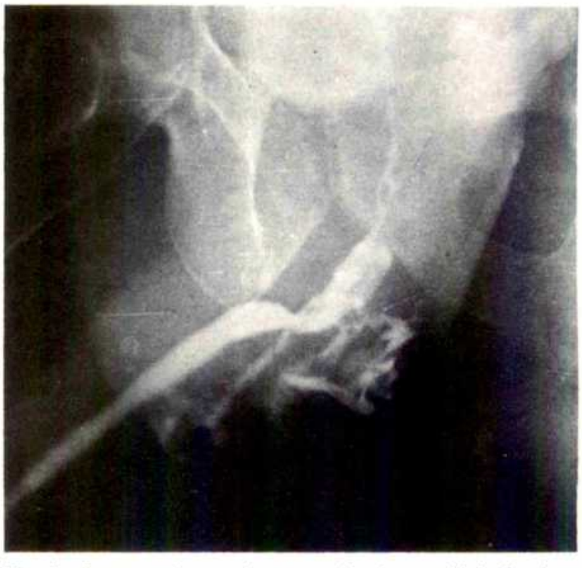

Fig. 1 Pre-operative urethrogram showing multiple fistulous tracts.

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Table Details of Patients

Patient	*Age (years)*	*Aetiology*	*Site of stricture*	*Duration*	*Mode of presentation*	*No. of urethrotomies and other procedures*	*Result*
K.V.K.	42	Gonococcal	Penile and bulbous urethra	6 years	Retention of urine, multiple urethral fistulas, openings over scrotum and perineum	Two direct vision internal urethrotomies over 4 months. Otis urethrotomy for penile stricture after 6 months	All fistulas healed within 8 weeks. Good stream. No recurrent fistulas over last 2½ years. Needs regular dilatations
R.P.M.	44	Inflammatory	Bulbous urethra	6 years	Oedematous and inflamed scrotal wall with multiple fistulas	Three DV internal urethrotomies over 2 months. Regular dilatation thereafter	All fistulas healed within 8 weeks. Scrotal wall returned to normal.
A.G.	40	Traumatic	Bulbous urethra	4 months	Periurethral abscess. Developed single fistula after drainage of abscess	One DVU	Fistula healed within 3 weeks after urethrotomy. No dilatation necessary
D.H.	45	Inflammatory	Bulbous urethra	1 year	Periurethral abscess. Poor urinary stream. Single fistula after drainage of abscess	One DVU	Single fistula healed within 2 weeks. No further dilatation necessary. Lost to follow-up after 6 months
R.Y.	40	Traumatic	Membranous urethra	6 months	Single fistula in perineum	One DVU	Fistula healed within 2 weeks. Good stream. Lost to follow-up after 1 year

DVU = direct vision urethrotomy

patients with single fistulous openings, the fistulous tracts healed spontaneously within 2 to 3 weeks after urethrotomy (Fig. 3) and no further dilatation was necessary.

One patient with multiple urethral fistulas had to undergo urethrotomy twice over 4 months. He also required an Otis urethrotomy for a distal penile stricture which developed 6 months later. In the other patient with multiple urethral fistulas, optical urethrotomy was done thrice over a 2-month period. In both of these patients the fistulas healed completely within 8 weeks. In the latter case the scrotum

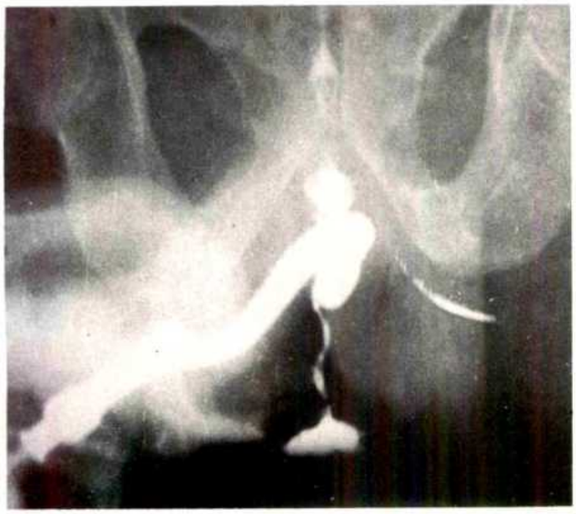

Fig. 2 Urethrogram showing single fistula after drainage of abscess.

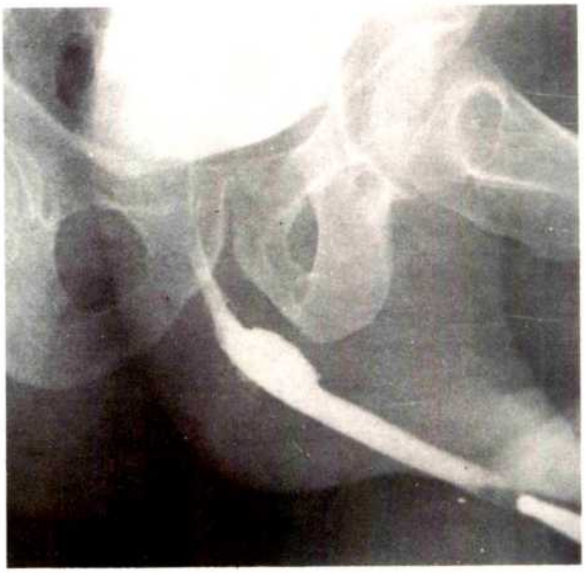

Fig. 3 Urethrogram 4 months after urethrotomy showing normal urethral calibre and no fistulous tracts.

returned to a normal size with the scrotal skin becoming soft and supple except for minimal scars at the sites where the abscesses were drained. These two patients have required regular dilatation over the last 2 years.

Three patients with single fistulas were followed up for 6 months to 2 years and none has had a recurrence.

Discussion

The use of optical urethrotomy in the treatment of urethral strictures has been reviewed and its success emphasised from time to time (Matouschek and Michaelis, 1975; Lipsky and Hubmer, 1977; Gaches *et al.*, 1979; Sacknoff and Kerr, 1980; Walther *et al.*, 1980; Bekirov *et al.*, 1982). It has been accepted as a valuable procedure for short strictures but poor results have been obtained in the presence of extensive periurethral disease (Walther *et al.*, 1980).

The standard treatment for urethral fistulas has been wide excision of the fistulous tract and openings in the urethra. For multiple urethral fistulas, wide excision of the urethral wall and periurethral tissues together with the fistulous tracts, followed by staged reconstructive procedures to close the defect, has been advocated (Nickel and Plumb, 1978).

The present series, though small, shows that closure of the fistulous tracts—single or multiple—can be achieved by optical urethrotomy alone provided that the urethral calibre can be restored. This has obviated the need for multi-stage urethroplasty procedures. In cases of multiple fistulas, urethroplasty would have involved wide excision of the fistulous tracts and surrounding fibrous tissues from the penoscrotal junction almost up to the ischial tuberosities, leaving a large defect difficult to cover up. Instead, satisfactory results have been obtained by optical urethrotomy without urethroplasty.

It is concluded that optical urethrotomy, if possible, is an adequate procedure in the management of urethral fistulas due to stricture.

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The Authors

S. B. Shah, MS, FRCS, Honorary Surgeon and Honorary Assistant Professor of Surgery.

V. G. Mehendale, MS, MNAMS(Ind), Honorary Surgeon and Honorary Assistant Professor of Surgery.

Requests for reprints to: S. B. Shah, Medico Surgical Clinic, Lakhani Nagar, Shastri Marg, Bombay 400 086, India.

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Carcinoma of Skin of Penis

W. I. B. ONUIGBO

Medical Foundation and Clinic, Enugu, Nigeria

Summary—Like the Jews, the Ibos or Igbos of Nigeria ritually circumcise males on the eighth day of birth. A retrospective review of approximately 15,000 surgical specimens collected from this ethnic group over a period of 13 years revealed 32 cases of carcinoma of the prostate but only 4 cases of penile carcinoma. One tumour arose on the glans penis. This localisation pattern suggests that, in circumcised males, smegma-induced squamous carcinoma of the glans can be abolished but not the ordinary squamous carcinoma that can develop by chance on the rest of the penis as well as on the glans. International urology would benefit from careful documentation of squamous carcinoma affecting various parts of the neonatally circumcised penile skin.

There is continuing controversy regarding penile carcinoma and circumcision (British Medical Journal, 1979; Kochen and McCurdy, 1980; Haas, 1981). Reports of squamous carcinoma have come from diverse communities but in circumcised Jews it is so rare that unusual malignancies are commoner (Girgis *et al.*, 1973).

In this study I report the few cases examined personally in a West African community with special reference to the Igbos, who constitute one of the three major ethnic groups in Nigeria and number about 15 million. The anthropologist, Basden (1966), who devoted a whole chapter to the similarities between Jewish and Igbo customs, wrote as follows: "Beginning with the infant, we have Circumcision. This rite is normally carried out on the eighth day after birth as in the case of the Israelites."

Patients and Methods

Between February 1970 and May 1983 I examined approximately 15,000 surgical specimens despatched to me with the appropriate clinical summaries by doctors working in government, missionary and private hospitals throughout Igboland. These were studied at central laboratories housed successively at the General Hospital, the Teaching Hospital and the Orthopaedic Hospital, Enugu, and a retrospective review was carried out with special reference to penile skin lesions, particularly carcinoma.

Results

The series contained 4 cases of penile skin carcinoma. These are analysed in Table 1. There were 26 benign penile lesions and 32 cases of prostatic carcinoma.

Table 1 Penile Skin Carcinoma in Circumcised Igbo Patients

Case	*Age (years)*	*Site*	*Duration (years)*	*Appearance*	*Histology*
1	55	Body	5	Ulcer	Squamous
2	68	Glans	2	Ulcer	Squamous
3	52	Root	2	Ulcer	Squamous
4	50	Body	7	Mass	Squamous

Discussion

Carcinoma of the penis is usually situated on the glans (Yu *et al.*, 1978; Cricco *et al.*, 1980). In the present series only one case exhibited this localisation. Hence, in the circumcised Igbo male, as in his Jewish counterpart (Girgis *et al.*, 1973; Persky, 1977), growths on the glans are rare.

What of the rest of the penis? Dodge and Linsell

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(1963) reported in their East African study that "most" carcinomas arose in the glans and did not specify the number arising in the rest of the organ. In the United States, Cricco *et al.* (1980) found 20 cases in the glans, 9 in the foreskin and 6 in the shaft. In Denmark, Jensen (1977) reported 37.8% in the glans, 31.7% in the coronal sulcus, 22.5% in the prepuce and 2.7% in the shaft. In the Far East, Yu *et al.* (1978) stated that 5.8% occurred in the prepuce, 63.4% in the glans, 25% in the glans and shaft and 5.8% in the shaft. Less precise were the data presented by Jackson (1966), Oluwasanmi *et al.* (1969), Khezri *et al.* (1978) and Narayana *et al.* (1982). However, it is clear that world-wide reports of penile carcinoma include growths in the shaft but indicate that it is a relatively uncommon site.

What is the significance of the reversed pattern found in Igbo patients? I believe that the answer lies in their circumcision status, because the half-mucosal character of the glans disappears with removal of the prepuce and it becomes covered by squamous epithelium (Haneke, 1982). Thereafter it is an area where squamous carcinoma can develop by chance, as in other skin areas. Such carcinomas are likely to occur less frequently than other chance growths of the penile body and root because of the relative extent of the surfaces at risk. Furthermore, the current concept is that with infant circumcision, carcinoma of the penis can be prevented. Infant circumcision guarantees prevention of smegma-induced carcinoma but not ordinary carcinoma of the penile skin.

Some queries arise concerning this series. Firstly, is squamous carcinoma of the skin in other sites a common condition in the Igbos? Okoro (1973) found that the incidence of skin tumours in relation to other skin diseases was only 0.5% in this locality, whereas in the United States it was 0.8%, in Mozambique 1%, in Algeria 2%, in Angola 2.8% and in Senegal 6.5%. Secondly, what is the average age at death of the population? Lifetime risk is important because the estimated median age of occurrence of penile cancer is 67 years (Kochen and McCurdy, 1980). The oldest patient in this series was only 68 but the average age at death is unknown here. However, Doll (1972) considered the distribution of cancer in rural Africa and the limitations of available data. His advocacy of proportional rates is relevant and Table 2 compares the age incidence of carcinomas of the penis and the prostate reported elsewhere (Onuigbo, 1984). It reveals that this series contains the older living cohorts and confirms that carcinoma of the glans penis is rare in the Igbos.

Table 2 Age Patterns of Igbo Patients with Carcinoma

Age (years)	*Penis*	*Prostate*
40-49	0	2
50-59	3	5
60-69	1	18
70-79	0	6
80	0	1

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The Author

W. I. B. Onuigbo, BSc, MD, PhD, FRCPath, Founder Director, Medical Foundation and Clinic, PO Box 1792, Enugu, Nigeria.

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Male Genital Injuries from External Trauma

A. S. CASS, P. GLEICH and C. SMITH

Department of Urology, St Paul-Ramsey Medical Center, St Paul; Urology Service, Hennepin County Medical Center, Minneapolis, USA

Summary—External trauma from a variety of causes, some unusual and bizarre, affect the male genitalia. Certain injuries are more common, have more severe consequences, or their management may be controversial. Seventy male genital injuries from external trauma are reported and include vacuum cleaner injuries, fracture of penis and the tourniquet syndrome.

The male genitalia may be involved in a wide variety of injuries from external causes. The usual causes include traffic accident, gunshot, burn, blow and crush, while the unusual include self-inflicted, sexual intercourse, avulsion (machinery), bite and the tourniquet syndrome. The causes, pathology and management of male genital injuries are reported in this study.

Patients and Results

Seventy male genital injuries are reviewed. Cases of testicular trauma, frenular tears and physician-performed circumcision mishaps were excluded.

Self-inflicted (17 Injuries)

Vacuum cleaner Eight men used a vacuum cleaner for sexual excitement: the suction end in seven and the motor (blade) end in one. The suction end caused extensive injury to the glans penis and urethra in five cases, including partial amputation in four. In all five cases the urethral loss was from 1 to 2 inches and was more extensive than the glans penis loss. The remaining two cases of suction end injury had superficial lacerations of the glans penis and urethra. The motor (blade) end injury resulted in complete amputation of the penis and the amputated glans was too macerated to allow anastomosis. Immediate repair was performed in six patients, delayed repair in one (patient delay 1 day) and conservative management was adopted in one patient.

Blade Four of the seven blade injuries resulted in superficial lacerations of the prepuce or glans penis and there were three severe injuries: one complete amputation and two partial amputations. Immediate repair was performed in four cases, delayed repair in one (patient delay 4 days) and expectant treatment was undertaken in two patients. Two of the superficial lacerations were attempts at circumcision; one was by an 18-year-old male and the other, while not self-inflicted, was premeditated by a father on his 2-week-old son with a razor blade for religious beliefs. The five other patients with blade injuries stated that the injury was accidental or inflicted by others on them. However, further questioning revealed that the injury was self-inflicted and psychiatric consultation and treatment were obtained. One of the superficial lacerations was caused by a blender. The complete amputation occurred in a 27-year-old who stated he was the victim of a sexual assault. The amputated penis was never found. On further questioning by the psychiatrist he admitted the injury was self-inflicted. One partial amputation occurred in a 63-year-old who was using a butcher's knife "to fashion wood" in the attic of his home while completely nude. The patient waited for 4 days before coming to hospital, where examination revealed an intact prepuce, and these facts indicated a self-inflicted injury rather than accidental, as stated by the patient. The other partial amputation occurred in a 59-year-old who claimed that his penis was accidentally caught in an electric fan. The amputated glans was not retrieved.

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Drill An electric drill was inserted by one patient through his external urinary meatus and immediate reconstruction of the glans penis was required.

Clothes peg A 51-year-old psychotic male applied a clothes peg to his upper scrotum to clamp the vas for sterilisation purposes. He presented after several weeks with infection and necrosis of the scrotum requiring debridement.

During Sexual Intercourse (4 Injuries) Three patients sustained a fracture of the penis. One presented immediately, one delayed 1 day, while the third presented after 4 weeks because the pain, swelling and deformity were not resolving. All underwent surgical repair of the torn tunica albuginea. The remaining patient sustained a superficial laceration at the base of the penis which was repaired.

Avulsion (Machinery) Injury (6 Injuries) Two injuries involved the skin of the penis and four involved the skin of the penis and scrotum. One was caused by a snow blower and five by machinery with an avulsion-type injury.

Primary debridement and reconstruction by suturing were attempted first and were successful in four cases. If the skin cover could not be obtained, then skin grafting of the denuded penis or burying the testicles under the skin of the upper thigh was performed in two cases.

Gun (10 Injuries) Seven gunshot injuries to the penis and two to the scrotum involved entrance and/or exit wounds only. Three were repaired and six were managed expectantly. One gunshot injury involved loss of skin of the scrotum which could be reconstructed after debridement.

Traffic (8 Injuries) Seven traffic accidents caused two contusions and five superficial lacerations to the penis or scrotum which were repaired. One traffic accident caused fractures of all rami of the pubic bones and the acetabulum with tearing of the suspensory ligament of the penis. This patient presented 11 years later complaining of ventral curvature of the penis on erection and a gap was palpable between the base of the penis and symphysis pubis which was surgically corrected.

Burns (3 Injuries) Debridement and daily dressings were used with the three patients with burns to the genitalia. Skin grafting was required later in one case of penile burns.

Bite (2 Injuries) The lacerations in the two patients were left open and managed by daily irrigation and dressings with systemic antibiotics.

Blow and Crush (17 Injuries) Six contusions and 11 lacerations to the genitalia requiring repair resulted from a variety of causes: fall on to an object (3), blade (3), toilet seat fell on it (2), caught in a zipper (2), hit angle iron (1), gored by a bull (1), kicked (1), ran into clothesline (1), between horse and barn (1), caught in a slammed door (1) and skiing (1).

Tourniquet Syndrome (3 Injuries) The two patients with penile tourniquet syndrome presented 2 years and 22 years later and required reconstructive surgery. One had a urethral fistula in the subcoronal area with a constriction ring around the penis just behind the glans and the mother admitted wrapping hair around the penis. The other presented with almost complete amputation of the penis except for an intact urethra. The mother stated "there was infection after circumcision at birth with an ulcer staying for a long time before it healed". A 37-year-old presented with acute strangulation of the penis and scrotum by a Timken ball bearing with which he had been masturbating. It took 3 h with emery discs on a dental drill to cut through the ball bearing in two places to allow its removal.

Discussion

Vacuum cleaner injury of the penis was first described by Fox and Barrett in 1960 and only 13 cases have been recorded in the English literature (Fox and Barrett, 1960; Hill, 1980; Forrest and Gillenwater, 1982). Eleven of these 13 cases involved the glans, shaft, external urinary meatus or prepuce of the penis with multiple lacerations which were sutured. Only two cases involved the corpora cavernosa and the corpus spongiosum with complete division or loss of the urethra proximal to the corona (Mendez *et al.*, 1972; Citron and Wade, 1980). Five of the seven suction end vacuum cleaner injuries in our study had extensive injury to the glans penis and urethra, including a urethral loss of 1 to 2 inches. There is no apparent explanation for the more extensive injury of the glans and urethra in our cases.

Acute traumatic amputation of the penis is managed initially by primary anastomosis or local reshaping measures (closure of open corpora and meatoplasty). Primary anastomosis is preferable if the distal segment is available, in good condition and the ischaemia time is less than 18 h (Engelman *et al.*, 1974). Longer ischaemia times may be possible with cooling of the severed phallus in iced saline solution and if successful microvascular re-anastomosis is performed.

Traumatic rupture of the corpus cavernosum of the penis (fracture of the penis) occurs if the erect penis impacts forcibly on a hard object (sexual partner's pubis, the floor, etc.), if it receives a direct blow or is subjected to abnormal bending. A cracking sound is heard, followed by penile pain, immediate detumescence and rapid swelling, discoloration and distortion. Deviation of the penis from the ruptured side eventually ensues. The lesion is a tear in the tunica albuginea of the corpus cavernosum with haemorrhage and haematoma formation. About one-third of the cases have an associated rupture of the urethra with urethral bleeding, haematuria and varying degrees of urinary extravasation. Management is controversial, since some advocate conservative treatment with an indwelling urethral catheter and pressure dressing (Ovrum, 1978), ice packs and oral streptokinase (Creecy and Beazlie, 1957), oxyphenbutazone and diazepam (Jallu *et al.*, 1980), or suprapubic cystostomy alone with associated ruptured urethra (Walton, 1979), while others advocate immediate surgical evacuation of the haematoma and primary repair of the ruptured corpus cavernosum (Gross *et al.*, 1977; Nymark and Kristensen, 1983). Some patients managed conservatively have experienced infection of the haematoma, permanent penile deformity, suboptimal erections, difficulty with coitus or a painful lump in the penis (Farah *et al.*, 1978; Walton, 1979; Jallu *et al.*, 1980; Pryor *et al.*, 1981; Bergner *et al.*, 1982). Our experience with three patients showed a better result in the two managed by immediate surgical repair. The third, managed conservatively, had persisting pain, swelling and deformity 4 weeks after injury.

Loss of penile skin by avulsion injury or burns is managed by split skin grafts after the denuded penis is clean and free of infection (Culp, 1977; Grewal *et al.*, 1982; Tripathi *et al.*, 1982). The avulsed skin should not be reapplied, for it invariably becomes necrotic and infected and must be subsequently removed.

With loss of scrotal skin the testicle should be housed in the remaining scrotal skin even though the reconstruction places it under considerable tension (Culp, 1977). Usually within a few months the scrotum will have returned to a nearly normal size. When insufficient scrotal skin prevents primary repair the testicles should be housed in thigh pockets superficial to the subcutaneous fat where the temperature parallels that of the scrotum (Culp, 1977).

All penetrating wounds to the male genitalia have the same principles of management—lavage, debridement and removal of foreign bodies, haemostasis, repair of the tissues, drainage and systemic antibiotics. Mechanical washing of the wound renders it free of contaminating micro-organisms and foreign bodies. Non-viable tissue should be removed until the cut edges show bleeding. Bleeding vessels should be ligated or cauterised. With a wound into the depths of the scrotum the testicles should be explored for bleeding and viability. The injured tissues should be repaired to restore them to as normal a relationship as possible, with adequate drains inserted. If there is gross contamination, the wound should be left open for delayed closure after infection has been eradicated. Wide spectrum systemic antibiotics should be given to combat mixed infection.

Traumatic rupture of the suspensory ligament of the penis has been recorded once in the literature and resulted from ventral deflection of the erect penis during sexual activity (Pryor and Hill, 1979). There was pain and swelling at the base of the penis. When erections returned after 15 months the penis did not assume the normal erect position and examination revealed a defect between the symphysis pubis and the base of the penis which would admit two fingers. Our patient had a similar deformity following a traffic accident with multiple fractures of the pubic bone. Pryor recommended surgical correction with nylon sutures placed between the symphysis and the tunica albuginea of the penis. The penis should be inflated with saline and if it fails to assume the normal erect position a further row of sutures should be placed more distally in the shaft of the penis (Pryor and Hill, 1979).

Zipper injuries consist of entrapment of the foreskin by the zipper fastener of the trousers. Extraction by manipulation of the zipper is usually prolonged, painful and sometimes successful (Watson, 1971). Manipulation under local anaesthesia was successful in our case. A bone cutting plier applied to cut the median bar or diamond of the zipper will result in the entire zipper falling apart with release of the entrapped foreskin (Saraf, 1982).

Patients with the penile tourniquet syndrome may present early with pain and swelling distal to the constricting agent or late with a urethral fistula and/or partial amputation of the penis. Acute strangulation of the penis has resulted from hair (Kerry and Chapman, 1973; Singh *et al.*, 1978; Bashir and El-Barbary, 1980), penile ring for erection enhancement (Fiumara, 1978), steel washer (McCally, 1979), metallic nut (Tiwari *et al.*, 1977;

Steiner, 1978), water tanks, bottles and pipes (Dakin, 1948). Late presentation with a urethral fistula and/or partial or near complete amputation has resulted from hair (Farah and Cerny, 1973; Thomas *et al.*, 1977; Singh *et al.*, 1978; Bashir and El-Barbary, 1980) and plastic ring (Stuppler *et al.*, 1973). Necrosis of the glans does not occur, despite the severity of the injury, because the slow progression of the constriction allows for the development of deep collateral circulation to the glans. The hair may be cut dorsally through the neurovascular bundle, sparing the urethra, or may transect the urethra, sparing sensation to the glans. Human hair is quite stretchable when wet and contracts when dry and can become buried in the skin of the penis and barely visible with the resulting swelling. Hair injuries of the penis should be considered whenever a circumcised boy presents with a swollen glans penis. A staged repair for the more severe injuries is recommended because the blood supply may be precarious (Thomas *et al.*, 1977). However, our patient had a successful result with a one-stage repair.

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The Authors

A. S. Cass, MB, BS, FRCS, Chief, Department of Urology, St Paul-Ramsey Medical Center, St Paul.

P. Gleich, MD, Clinical Instructor, Department of Surgery, University of Minnesota, Minneapolis; Staff Urologist, St Paul-Ramsey Medical Center, St Paul.

C. Smith, MD, Clinical Instructor, Department of Surgery, University of Minnesota, Minneapolis; Staff Urologist, Hennepin County Medical Center, Minneapolis.

Requests for reprints to: A. S. Cass, Department of Urology, St Paul-Ramsey Medical Center, 640 Jackson Street, St Paul, Minnesota 55101, USA.

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Haemoglobin F Levels in Patients with Testicular Tumours

A. AKDAS, E. KANSU, Z. KIRKALI, D. REMZI and D. FIRAT

Department of Urology, Division of Haematology-Oncology and Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey

Summary—This study was designed to examine haemoglobin F levels prior to therapy in 39 patients with testicular tumours (10 seminoma, 29 non-seminomatous tumours) and 20 controls. HbF levels were significantly increased in the group with testicular tumours ($1.66 \mp 0.12\%$) compared with normal controls ($0.99 \mp 0.08\%$) ($P < 0.001$). Non-seminomatous tumours had more pronounced levels than seminomas ($P < 0.001$). No correlation was found between HbF level and stage of the disease. We suggest that HbF production could be significantly reactivated in adult patients with testicular tumours and may be a useful marker.

Fetal haemoglobin (HbF), which makes up 75 to 90% of total haemoglobin at birth, gradually decreases until the normal adult level is attained in the circulating red cells. The factors which play a role in this decline are not well known (Bunn *et al.*, 1977). HbA ($\alpha_2\beta_2$) gradually replaces HbF ($\alpha_2\gamma_2$) after birth. Increased HbF levels have been reported in patients with sickle cell anaemia, thallasaemia (Wood *et al.*, 1975), acute and juvenile chronic myeloid leukaemia (Walker and Ali, 1973; Weatherall *et al.*, 1975), lymphoma and in a variety of solid tumours (Kazazian, 1974; Chudwin *et al.*, 1977). We have previously reported increased levels of HbF in patients with urogenital cancers (Müderrisoğlu *et al.*, 1983).

This study was designed to examine the HbF levels prior to therapy in patients with testicular tumours and to compare and correlate the levels with histological type and stage of the disease.

Patients and Methods

Since our last report (Müderrisoğlu *et al.*, 1983) we have studied 39 new patients with testicular tumours with proven histological diagnosis. All of the surgical tissue biopsy samples were examined after haematoxylin and eosin staining. The histological type of the tumour and stage of the patients are presented in Table 1. Staging was based on the system proposed by Boden and Gibb (1951) and bilateral retroperitoneal lymphadenectomy was performed on patients with stage I and II non-seminomatous tumours. All blood samples were drawn from the patients prior to therapy and from 20 age- and sex-matched normal control subjects. Haematological assessment, including complete blood count, reticulocyte counts and differential counts, was performed using standard techniques (Brown, 1976). The level of HbF was determined by the alkali-denaturation method using a modification of the assay described by Betke *et al.* (1959). In 10 patients and 20 controls HbF was hetero-

Table 1 Distribution of Patients According to Stage and Histopathological Type

	Stage			
Histological Type	*I*	*II*	*III*	*Total*
Seminoma	3	3	4	10
Non-seminomatous tumours	9	10	10	29
Total	12	13	14	39

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geneously distributed among the red cells and none of the subjects exhibited features compatible with hereditary persistence of fetal Hb and other types of haemoglobinopathies.

Results

HbF levels in normal controls had a mean value of $0.99 \mp 0.08\%$ (range 0.5-1.7). The patients with testicular tumours had significantly elevated levels of HbF ($1.66 \mp 0.12\%$) compared with normal subjects ($P<0.001$) (Table 2). When this group was analysed according to the histopathological diagnosis, both seminomas and non-seminomatous subtypes had significantly elevated levels of HbF ($1.25 \mp 0.6\%$ and $1.80 \mp 0.15\%$ respectively) compared with controls. Non-seminomatous tumours had higher HbF values than seminomas ($P<0.02$) (Table 2).

On examining the possible correlation of HbF levels with the stage of the disease, it was observed that HbF production was significantly increased in all stages of the testicular tumours compared with the controls ($P<0.001$) (Table 3). Within the three stages, no correlation was detected between HbF levels and the stage of the disease ($P>0.05$).

Table 2 Haemoglobin F Levels in Testicular Tumours

Group	*n*	$\bar{x} \mp S\bar{x}\%$ *(range)*	*Statistical significance*
Normal	20	0.99 ∓ 0.08 (0.5%-1.7)	$P<0.001$
Testicular tumours	39	1.66 ∓ 0.12 (0.5%-3.6)	
Seminoma	10	1.25 ∓ 0.16* (0.5%-2.0)	$P<0.02$
Non-seminomatous tumours	29	1.8 ∓ 0.15† (0.6%-3.6)	

* Significant, $P<0.02$, compared with controls.
† Significant, $P<0.001$, compared with controls.

Table 3 Haemoglobin F Levels in Testicular Tumours According to Stage of the Disease

Groups	*n*	$\bar{x} \mp S\bar{x}\ \%$	*(range)* (%)
Normal	20	0.99 ∓ 0.08	(0.5-1.7)
Stage I	12	1.56 ∓ 0.22*†	(0.5-3.3)
Stage II	13	1.80 ∓ 0.22*†	(0.75-3.2)
Stage III	14	1.62 ∓ 0.21*†	(0.5-3.6)

* Significant, $P<0.001$, compared with controls.
† Not significant, $P>0.05$, compared with other stages.

Discussion

Elevated levels of alkali-resistant (fetal) haemoglobin have been found in various types of cancer patients (Kellen *et al.*, 1980). This study has shown that HbF production can be increased in untreated patients with testicular tumours. In our previous report we observed the elevation of HbF in a limited number of patients with both histological types of testicular tumour (Müderrisoğlu *et al.*, 1983). The present study has extended our observations and has indicated that non-seminomatous tumours may have significantly elevated levels of HbF compared with seminomas. This elevation does not seem to be affected by the extent of the disease.

In parallel, previous studies (Chudwin *et al.*, 1977; Dainiak and Hoffman, 1980) revealed increased HbF levels measured by different techniques in patients with testicular tumours. It was shown in these studies that HCG and AFP production were not uniformly related to the elevated HbF levels. Although there have been several attempts to correlate the cell types of the onco-fetal products and the HbF synthesis, no definitive mechanism has been shown to elucidate the enhancement of HbF synthesis in various types of solid tumours (Bunn *et al.*, 1977; Dainiak and Hoffman, 1980; Kellen *et al.*, 1980).

It is apparent that more basic studies are required to explain this acquired "switch" in human haemoglobin synthesis. Meanwhile, we postulate that fetal haemoglobin production may still represent an abnormal proliferation of a clone of stem cells affected by tumour or tumour-derived products.

It is suggested, therefore, that HbF production could be significantly reactivated in adult patients with testicular tumours and may be a useful marker for these tumours. We are now studying the chain analysis and molecular characterisation of HbF in this particular group of patients.

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The Authors

A. Akdas, MD, Associate Professor of Urology.
E. Kansu, MD, FACP, Associate Professor of Haematology.
Z. Kirkali, MD, Research Assistant in Urology.
D. Remzi, MD, Professor of Urology.
D. Firat, MD, Professor of Internal Medicine.

Request for reprints to: E. Kansu, Division of Haematology-Oncology, Hacettepe University School of Medicine, Ankara, Turkey.

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Ascent of the Testis: Fact or Fiction

J. D. ATWELL

Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, Southampton

Summary—Ascent of the testis from the normal to an undescended position has been observed in 10 patients. In 9 of them there was a complete hernial sac and it is suggested that the acquired malposition of the testis is due to partial absorption of the processus vaginalis into the parietal peritoneum. Alteration in the length of the inguinal canal with growth may be an additional contributory factor. The mean interval between the original and subsequent observations was 5.2 years, leading to a late orchiopexy at a mean age of 9.4 years.

Maldescent of the testis is one of the commonest conditions of infancy and childhood and may be related to alterations in the fate of the processus vaginalis (Fig. 1). Mistakes in the diagnosis of the position of the testis are not unusual despite its superficial position and may lead to an unnecessary orchiopexy. Adhesions resulting in the fixation of the testis in an abnormal position are a well known preventable complication of inguinal herniotomy. Ascent of the testis without previous surgical interference is uncommon and is not mentioned in two monographs on the undescended testis (Scorer and Farrington, 1971; Fonkalsrud and Mengal, 1981) but has been reported in a series of 4300 testes examined at birth, 1 year and 3 years of age (Villumsen and Zachau-Christiansen, 1966). In 69 of these patients 87 of the testes were found to be higher at 3 years of age than at 1 year of age. Such observations have usually been attributable to observer error. The purpose of this report was to present the clinical findings in 10 patients where ascent of the testes occurred and to discuss an explanation for the observation.

Patients

No. 1. M.B. was born in 1976 with posterior urethral valves. Initially the testes were in the scrotum and this was recorded on several occasions. On review in 1981 the left testicle was palpable in the groin. At operation on 20 October 1981 a left orchiopexy was performed, when a complete inguinal hernial sac was found and excised and the testis was placed in a dartos pouch in the scrotum.

No. 2. B.I. was born in 1973. His father (a doctor) and his mother (a nurse) stated that in his early life both testes were palpable in the scrotum. At 6 years of age the testes were noted to be in the scrotum by a consultant surgeon. In 1981 he was reviewed and both testes were palpable in the superficial inguinal ectopic position. At operation a bilateral orchiopexy was performed after isolating, transfixing and excising complete hernial sacs.

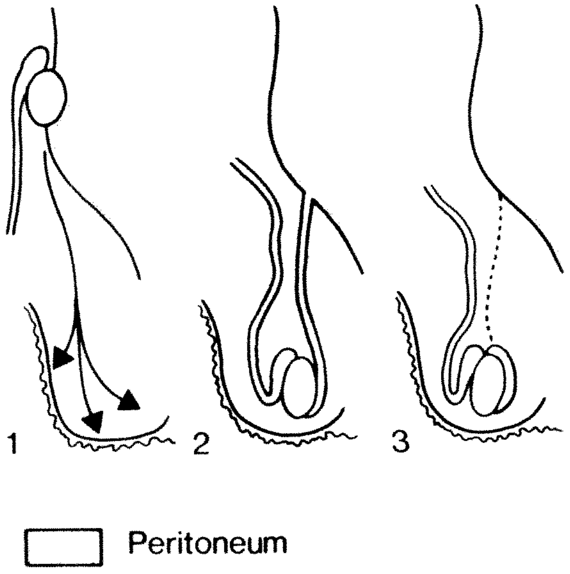

Fig. 1 Pathway of descent of the testis posterior to the processus vaginalis.

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No. 3. A.H. was born in 1970. At 9 years of age the testes were palpable in the scrotum Four years later the left testis was found to be "tethered" and could easily be manipulated to the neck of the scrotum. At operation in 1983 a left orchiopexy revealed a thin walled complete hernial sac. The testis was then placed in a satisfactory position in the scrotum.

No. 4. S.S. was born in 1969. In 1973 he was referred for circumcision and the testes were palpable in the scrotum. In 1974 he was reviewed again because of constipation and the testes were noted to be in the scrotum. A similar finding was noted in 1976. In 1983 he was referred again and examination revealed a right undescended testis and a left varicocele. A right orchiopexy was performed and the testis was biopsied. The left varicocele was ligated and excised and the testis was biopsied. The biopsy of the left testis was normal with a fertility index of 100% compared with 60% for the right testis.

No. 5. J.I. was born in 1976. He was repeatedly examined in 1978, 1979, 1980 and 1981 and the testes were recorded as fully descended. In 1982 the left testis was normal but the right testis was tethered at the neck of the scrotum. In 1983 a right orchiopexy was performed; a complete hernial sac was found and excised and the testis was placed in a satisfactory position in the scrotum.

No. 6. W.S. was born in 1976. In 1977 the left testis was found to be in the scrotum but the right was high and could not be palpated and the right side of the scrotum was hypoplastic. The examination was repeated in 1978 and, as the findings were similar, a right orchiopexy was undertaken. He was reviewed in 1983 and the right testis was in a satisfactory position but the left was now at the neck of the scrotum. A left orchiopexy was performed; a complete hernial sac was excised and the testis was mobilised and placed in a satisfactory position in the scrotum.

No. 7. S.H. was born in 1972. In 1980 when admitted to an E.N.T. ward and in 1981 when admitted following a head injury the testes were recorded as scrotal in position. In 1983 he was referred because of a right undescended testis and this was found to be at the neck of the scrotum. A right orchiopexy was performed and a complete hernial sac was found and excised and the right testis was then fixed in the scrotum.

No. 8. M.N. was born in 1973. In 1977 he was seen in another hospital because he had a left hydrocele. The right testis was normal. A further examination by a surgical consultant 2 years later confirmed the normal position of the right testis. At the age of 10 years he was seen again and examination showed that the right testis was in the inguinal region. At operation in 1983 a complete hernial sac was found and a right orchiopexy was performed.

No. 9. P.D. was born in 1974. In 1979 when examined the testes were easily manipulated into the scrotum. (Right retractile: left normal). Examination in 1984 demonstrated that the right testis was in the groin and the left was in the scrotum in a normal position. At operation a complete hernial sac was found on the right and an orchiopexy was performed.

No. 10. H.C. was born in 1974. At 4 years of age he was referred because of preputial adhesions. At that time the testes were normally descended in the scrotum. He was referred at 10 years of age for a left undescended testis. On examination the left testis was found tethered at the neck of the scrotum. At operation a complete hernial sac was isolated, transfixed and excised and the testis was placed in a satisfactory position in the scrotum.

Results

The testis which moved upwards was on the right in 5 cases, on the left in 4 and bilateral in 1. In all patients the testis had previously been noted to be in a normal position, often by several observers. The time interval between the testis being found in a normal position and being found high ranged between 2 and 10 years with a mean of 5.2 years. The ages of the patients at their eventual orchiopexies ranged between 5 and 14 years with a mean of 9.4 years (Table). In most patients the change in position of the testis occurred between 7 and 13 years of age. At operation the commonest finding was a complete hernial sac (9 patients). None of the patients presented with clinical evidence of an inguinal hernia.

Discussion

These case reports highlight several features which require discussion. The first is whether there was any observer error to account for the alteration in the position of the testis. In all of our patients the position of the testis was recorded in the notes when the patient was referred or admitted for other reasons, *e.g.* following trauma, acute abdominal pain, circumcision, etc. In the past, if a child attended and was found to have an undescended testis and the parents were adamant that the testis had been in the scrotum, their statement was usually ignored and the physical findings on the day of examination were accepted as an indication for orchiopexy. There is no doubt that there can be observer error in assessing the position of the testis because of its mobility and retractibility.

Alterations in the shape of the pelvis and the length of the inguinal canal occur with growth and these may be factors which lead to movement upwards of the testis. In the young infant the

Table

Case no.	*Side*	*Time between initial exam. and operation (years)*	*Age at operation (years)*	*Type of hernial sac*
1	Left	5	5	Complete
2	Bilateral	2	8	Complete
3	Left	4	13	Complete
4	Right	10	14	Incomplete
5	Right	5	7	Complete
6	Left	6	7	Complete
7	Right	2	9	Complete
8	Right	7	11	Complete
9	Right	5	10	Complete
10	Left	6	10	Complete
Mean		5.2	9.4	

inguinal canal is short and the internal and external rings are almost in an antero-posterior position. As the child grows the obliquity and length of the inguinal canal change and it may measure up to 4.5 cm in length. It is well known that the true pelvis is absent in the young female infant and that this accounts for the high incidence of finding an ovary or even the fallopian tube in an inguinal hernial sac (Atwell, 1962). After the age of 2 years this is unusual.

An explanation for the ascent of the testis is that the peritoneum of the processus vaginalis becomes absorbed to form part of the parietal peritoneum (Fig. 2). This alteration in the distribution of the peritoneal lining of the abdominal cavity leads to traction on the cord and ascent of the testis. Similarly with an incomplete hernial sac, the fibrous band remaining from the obliterated processus vaginalis which joins with the tunica vaginalis may lead to ascent of the testis.

A clinical feature of interest in these patients was that despite the persistence of a complete hernial sac in 9 of the 10 patients, none of them had clinical evidence of an inguinal hernia. Thus it seems prob-

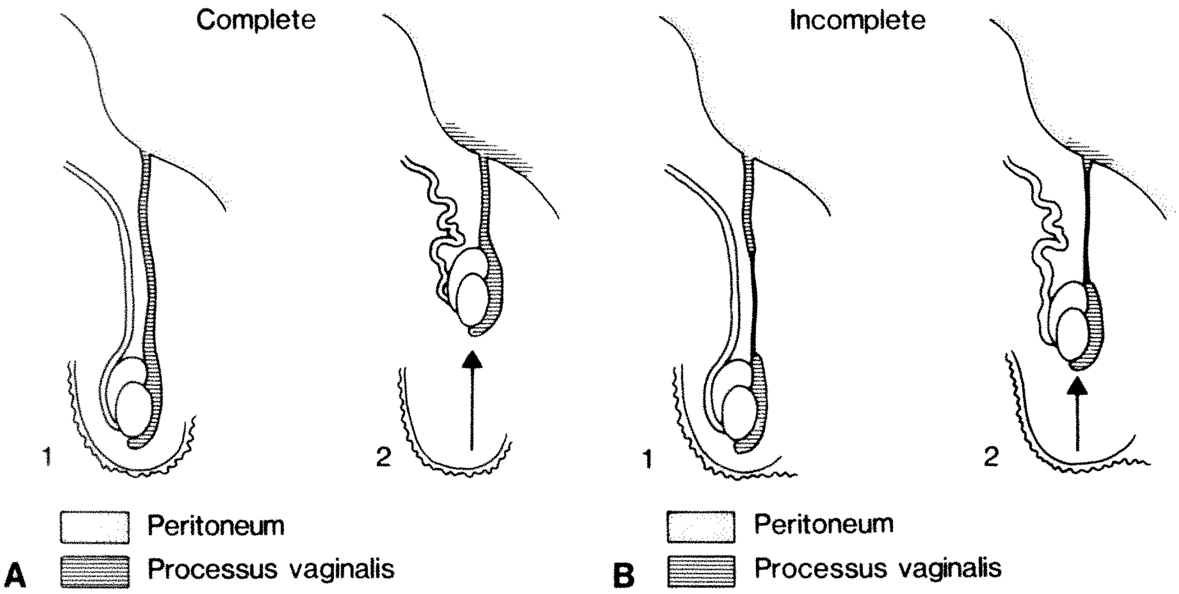

Fig. 2(A and B) Diagram to show the possible absorption of the processus vaginalis to become part of the parietal peritoneum with resultant shortening of the cord and testicular ascent.

able that the development of a hernia in adolescence and young adults may be along a pre-existing hernial sac; our findings would support this hypothesis.

Ascent of the normally descended testis is unusual and we have encountered only 10 examples. This contrasts with over 1000 orchiopexies performed over a similar 13-year period. It is possible that the incidence of testicular ascent may be higher, as one has often ignored previous recorded findings on clinical examination or the history elicited from the parents. In the management of the patient it is difficult to see how this situation can be prevented. This is unfortunate as the average age of 9.4 years at the time of the orchiopexy is far from ideal. Our aim is that this operation should be performed by 2 years of age. Obviously, if there are doubts about the position of the testis at any clinical examination, long-term surveillance becomes obligatory.

Acknowledgments

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The Author

J. D. Atwell, FRCS, Consultant Paediatric Surgeon, Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, East Wing, Shirley, Southampton S09 4XY.

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Survey of Antibiotic Prophylaxis in British Urological Practice

N. I. L. WILSON and H. J. E. LEWI

Department of Urology, Royal Infirmary, Glasgow

Summary—Guidelines for the use of prophylactic antibiotics to cover operative procedures on the urinary tract have been suggested, but the extent to which these have been adopted into routine practice has not been assessed.

This survery documents the use of prophylactic antibiotics in urological surgery in Britain. It demonstrates that awareness of the potential role of antibiotic prophylaxis is increasing. Most urologists now adopt a selective approach in the use of prophylactic agents.

There are now established principles to govern the use of prophylactic antibiotics. The chosen antibiotic ought to be effective against the pathogens likely to be present. The mode of administration should be designed to achieve high tissue levels at the time of surgery without provoking toxicity or encouraging the emergence of resistant organisms.

The problems of infection in urological practice differ from those seen in general surgery, since endoscopic procedures predominate and transabdominal operation are usually extraperitoneal. Nevertheless, bacteraemia and septicaemia from genitourinary tract procedures are well documented and form a common basis for the use of prophylactic antibiotics. In a study involving the major hospitals in Pennsylvania, operative procedures involving the urinary tract were the most common reason for antibiotic prophylaxis (Shapiro *et al.*, 1979).

Suggestions regarding the necessity for antibiotic prophylaxis in various areas of urological surgery have been made but conflicting results have been obtained (Chodak and Plaut, 1979) and the role is confused; nevertheless, guidelines have been proposed (Chisholm, 1982; Russo *et al.*, 1983).

The extent to which these measures have been incorporated into routine practice has not been assessed. We therefore sent a postal questionnaire to urologists in Britain asking for details of their use of prophylactic antibiotics.

Methods

In 1983 postal questionnaires were sent to all consultant urologists and surgeons with a significant interest in urology throughout Britain. They were asked for details of their use of antibiotic prophylaxis in patients undergoing surgery (Table 1). Urologists who used prophylactic antibiotics were asked to give their choice of antibiotic, the timing and route of administration, and the duration of cover provided. Those who adopted a selective policy were asked to indicate the basis of their selection, and those who did not use routine antibiotic cover were asked to give their reasons. Additional comments were welcomed.

Results

Of the 209 questionnaires circulated, 166 (79%) were returned.

Seventeen per cent of urologists used routine antibiotic prophylaxis during surgery for renal stone disease (Table 2), 8% for ureterolithotomy and 13% for bladder stone surgery. Thirty-four per cent routinely covered prostatic biopsy but only 5% used routine antibiotic prophylaxis for cystos-

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Table 1 Use of Antibiotic Prophylaxis in Patients Undergoing Surgery

Surgical options	*Basis for selective policy*	*Reasons for NOT using prophylaxis (all options)*
(i) Surgery for stone disease in kidney, ureter and bladder	Significant MSSU Type of stone Systemic upset	(i) Low incidence of infective complications
(ii) Prostatic biopsy	Route of biopsy	(ii) Lack of proof of efficacy
(iii) Cystoscopy	Significant MSSU Previous febrile reaction	(iii) Cost versus benefit
(iv) TURP	Significant MSSU Catheter	(iv) Encourage the emergence of resistant organisms
(v) Open prostatectomy	Significant MSSU Catheter Surgical approach	

Table 2 Use of Prophylactic Antibiotics. (% of Urologists who Responded)

	Routine	*Selective*	*Never*
Stone disease			
Renal	17	79	4
Ureteric	8	79	13
Bladder	13	80	7
Prostatic biopsy	34	22	44
Cystoscopy	5	70	25
TURP	10	80	10
Open prostatectomy	8	81	11

(166 questionnaires were returned)

Table 3 Reasons Given by Urologists who Never Used Prophylactic Antibiotics. (More than One Reason was Acknowledged)

	% Urologists
Low incidence of infective complications	80
Lack of proof of efficacy	26
Cost versus benefit	15
Possible development of resistance	11

copy, 10% for transurethral resection of prostate (TURP) and 8% for open prostatectomy.

The commonest reason for not using prophylactic antibiotics (Table 3) was that the incidence of infective complications was too low (80%). Other reasons were lack of proof of the efficacy of prophylactic antibiotics (26%) and considerations of the cost (15%). Concern over the encouragement of bacterial resistance was the least frequent reason (11%) for avoiding antibiotics.

A selective policy was adopted by approximately 80% of urologists in using antibiotic cover for stone disease surgery (Table 2). A similar proportion adopted this practice when carrying out cystoscopy (70%), TURP (80%), or open prostatectomy (81%). A selective policy was less common in prostatic biopsy (22%).

Stone Disease

Thirty-six urologists always used prophylactic antibiotics to cover stone surgery in some part of the urinary tract. In those who used a selective policy the usual indication (Table 4) was a significant urine culture from the midstream specimen of urine (MSSU; 91%) but when operating for staghorn

Table 4 Indication for Use of Prophylactic Antibiotics by Urologists Using a Selective Policy (%)

	Stone disease (n = 131)	*Prostatic biopsy (n = 36)*	*Cystoscopy (n = 116)*	*TURP (n = 133)*	*Open prostatectomy (n = 132)*
MSSU	91	6	95	92	93
Catheter	1	—	3	42	43
Indication related to procedure (see text)	15	83	51	—	—

calculus 15% of urologists would give cover whatever the urine culture. In the absence of a specific indication the majority based their policy on the post-operative course. The parenteral route of administration was used by 84% (Table 5). Fifty-three per cent continued antibiotics for longer than 48 h (Table 6).

Prostatic Biopsy

Only 22% of urologists adopted a selective policy for prophylactic antibiotics in prostatic biopsy. Of these, 83% based their policy on the approach used to obtain the biopsy. Sixty-seven per cent gave cover if using the transrectal approach and 17% if using the transperineal route. Unfortunately the design of the questionnaire did not identify the approach used by those who either routinely prescribed antibiotics to all or those who never used them. Seventy per cent used the parenteral route for adminstration (Table 5) and 51% employed a single dose prior to biopsy (Table 6). Ten per cent did not commence therapy until after the biopsy.

Cystoscopy

A selective policy was used by 70% of urologists for cystoscopy and a significant MSSU culture was the usual reason (95%). Fifty-one per cent (Table 4) accepted a previous febrile reaction when undergoing cystoscopy as an indication for antibiotic cover. The parenteral route was used by 77% (Table 5) and 33% continued treatment longer than 48 h (Table 6).

Table 5 Route of Administration of Antibiotics. (% of Urologists giving Details)

	Route	
	IV/IM	*Oral*
Stone disease (n = 100)	84	16
Prostatic biopsy (n = 86)	70	30
Cystoscopy (n = 88)	77	23
TURP (n = 99)	75	25
Open prostatectomy (n = 87)	77	23

TURP

The most frequent indication given by those who employed a selective policy (80%) was a significant pre-operative urine culture, but the presence of a catheter was also regarded as sufficient indication for prophylaxis (Table 4). Parenteral administration was used by 75% (Table 5) and 45% gave antibiotics for longer than 48 h (Table 6). Fifteen per cent continued therapy whilst a catheter was *in situ*.

Open Prostatectomy

A significant MSSU culture was the usual indication for antibiotic cover mentioned by those who were selective in their use of antibiotics and, as with TURP, a lesser proportion (43%) used them in the presence of a catheter alone. The precise surgical procedure had little bearing on the use of antibiotics as only 3% felt prophylaxis was indicated with a retropubic approach and 2% with a transvesical approach. The parenteral route predominated (77%) and 44% give antibiotics for longer than 48 h. Ten per cent continued therapy whilst a catheter was *in situ*.

Preferred Antibiotics

The most popular prophylactic agent was an aminoglycoside (42%), usually gentamicin, and this popularity applied to each of the five surgical options. Co-trimoxazole was also popular (Table 7). Combinations of more than one antimicrobial were selected by 7% and consisted of gentamicin together with co-trimoxazole, a penicillin or metronidazole.

Table 6 Timing and Duration of Antibiotic Administration. (% of Urologists giving Details)

	>24 Pre ± Post	*<24 Pre ± Post*			
		SD	*<48 Post*	*>48 Post*	*Post only*
Stone disease (n = 100)	14	8	18	53	7
Prostatic biopsy (n = 86)	2	51	22	16	10
Cystoscopy (n = 88)	7	23	21	33	16
TURP (n = 99)	9	15	18	45	13
Open prostatectomy (n = 87)	14	8	21	44	13

SD = single dose.

Table 7 Preferred Antibiotics Used for Prophylaxis. (% of Urologists giving Details)

Aminoglycoside	42
Co-trimoxazole	31
Cephalosporin	16
Ampicillin	15
Metronidazole	3
> 1 agent used	7

Discussion

The occurrence of post-operative infective complications is of major concern to all urologists. The failure of modern aseptic techniques to reduce the incidence of wound infection, bacteraemia and bacteriuria has led to continuing interest in the concept of antibiotic prophylaxis.

A critical review of the literature on prophylaxis in urological operations was frustrated by the conflicting results reported (Chodak and Plaut, 1979). More recent studies have produced more reliable data and guidelines for the use of prophylactic antimicrobials have been put forward (Chisholm, 1982; Russo *et al.*, 1983).

Our response rate (79%) was adequate and permitted the documentation of the current use of prophylactic antibiotics in British urological practice. It is clear that the role of antibiotic prophylaxis remains confused and that a standard format has not been achieved. Prophylaxis is aimed at providing short-term cover for the operative period—usually for 48 h or less in the peri-operative period. Continuation of therapy for longer than this is in effect a treatment policy. Similarly, whilst a selective policy may be a more cost-effective method, it tends towards treatment rather than prophylaxis. A selective approach was used by approximately three-quarters of urologists in all situations except prostatic biopsy, where less than a quarter adopted this method.

Removal of intrarenal stones may be associated with a wound and urinary tract complication rate ranging from 5 to 30% (Maddern, 1967; Wickham and Mathur, 1971; Boyce and Elkins, 1974). The risk of septicaemia during manipulation of the stone is high, and this has been effectively reduced by antibacterial prophylaxis (Chisholm, 1982). Only 17% used routine prophylactic antibiotics and the majority relied on selection, using the MSSU for guidance, yet it has been shown that whilst the MSSU may be sterile the pelvic urine or the stone itself may be infected and still constitute a high risk group that cannot be identified pre-operatively (Lewi *et al.*, 1984).

The routine use of antibiotics was more common in prostatic biopsy than in the other situations we studied. Following prostatic biopsy by the transrectal route, between 5 and 40% of patients have infective complications and the routine use of antibiotics has been recommended (Chisholm, 1982; Russo *et al.*, 1983). The use of a povidone iodine enema in transrectal prostatic biopsy has been studied with encouraging results (Brown *et al.*, 1981) and its use is now advocated in this procedure (Chisholm, 1982), but only one urologist used this measure. The transperineal route has a lower incidence of infective complications and the routine use of antibiotics may offer no advantage if the urine is sterile (Packer *et al.*, 1984).

The pattern of usage in the other surgical procedures demonstrated the popularity of a selective antibiotic policy. About three-quarters of urologists used the presence of urinary infection as a means of selecting a high risk group when undertaking cystoscopy or prostatic surgery. However, a urinary tract infection may have no specific symptoms and a system that allows a current urine culture report to be available prior to surgery is essential. A post-operative urinary tract infection will influence the post-operative course in all forms of prostatectomy (Singh *et al.*, 1973). A number of early studies on the use of antimicrobial prophylaxis directed towards reducing post-operative bacteriuria after TURP can be criticised because of poor design (Chodak and Plaut, 1979). Recent studies have produced more reliable data. Using short courses (48 h) starting pre-operatively, cephradine (Williams *et al.*, 1980), cefotaxime (Hargreave *et al.*, 1982), co-trimoxazole, cephalexin, mecillinam and cefoxitin will all reduce bacteriuria after TURP (Bannister *et al.*, 1981; Nielsen *et al.*, 1981; Shah *et al.*, 1981). Chisholm (1982) advised that all patients undergoing TURP should have short-term antibacterial prophylaxis, but only 10% of urologists have adopted this approach.

Forty-two per cent of urologists indicated that their preferred antibiotic was an aminoglycoside, with parenteral administration being the preferred route. Co-trimoxazole was used by 31% and a cephalosporin by only 16%. Second and third generation cephalosporins have a broad spectrum of activity and are recognised as safe; however, the traditional choice of an aminoglycoside as effective treatment of septicaemia ensures its popularity when an agent for prophylaxis is being selected.

The information given for timing and duration of antibiotic administration indicated that many urologists adopted regimens related more to treatment than prophylaxis. The overall pattern for prostatic biopsy was closest to the accepted principles of prophylaxis and there was a clear tendency to use short-term cover, with half employing a single dose. The pattern differed for the other situations. Fourteen per cent of surgeons commenced antibiotic therapy prior to the day of surgery and in up to 50% of cases therapy was continued for longer than 48 h post-operatively. There is no doubt that a longer peri-operative regimen of antibiotic therapy encourages the emergence of resistant organisms without conferring additional benefit. Sixteen per cent of surgeons commenced antibiotic treatment in the post-operative period, which resulted in the treatment of post-operative complications rather than preventing the complications.

Most urologists who never used antibiotic prophylaxis stated that the incidence of infective complications in their practice was too low to warrant its use. It is well recognised that most surgeons tend to underestimate the incidence of such problems unless they are undertaking a prospective assessment. Also, a prospective evaluation of post-operative complications, even in the absence of antimicrobial prophylaxis, significantly reduces the complication rate, indicating that an awareness of post-operative problems will result in a reduction in their incidence rate.

This survey has documented the use of prophylactic antibiotics in urological surgery in Britain. In general, an awareness of the potential role of antibiotic prophylaxis is increasing and most urologists now adopt a selective approach.

Acknowledgement

We thank colleagues throughout Britain who completed and returned the questionnaires.

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The Authors

N. I. L. Wilson, FRCS(Glas), formerly Registrar in Urology, Royal Infirmary, Glasgow. Now Orthopaedic Registrar, Western Infirmary, Glasgow.

H. J. E. Lewi, FRCSE, Senior Registrar in Urology, Royal Infirmary, Glasgow.

Requests for reprints to: N. I. L. Wilson, Department of Orthopaedic Surgery, Western Infirmary, Glasgow G11 6NT.

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AUTHORS' FOLLOW-UP

Single Sample Estimates of Renal Clearances

A. R. CONSTABLE, M. M. HUSSEIN, M. P. ALBRECHT, F. D. THOMPSON, P. E. PHILALITHIS and A. M. JOEKES

Institute of Urology and St Peter's Hospitals, London

The methods outlined in our original report (Constable *et al.*, 1979) remain valid simplifications for the measurement of effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) for routine clinical purposes. They provide at least a guide to the state of the patient's renal function and, if all of the obvious precautions are taken (accurate sample timing, avoiding extravasation, *etc.*), the results are as accurate as most of the well established multiple sample techniques.

The methods described make use of a 44-min blood sample for the ERPF and a 3-h sample for the GFR. Long practice with the technique has confirmed the need to have the patient resting for up to half an hour before the injection and to continue resting until the 44-min sample has been taken. This will produce an ERPF value which may differ from the patient's true ERPF when in a normally active state, but more reliable and repeatable results are obtained.

It is our normal practice to give a combined dose of ^{125}I Hippuran and ^{51}Cr EDTA. As described in our original study, the GFR is then determined from the "volume of distribution" calculated from the 3-h blood sample. In practice, however, a single sample method can sometimes go badly wrong. Failure to take the sample at exactly 3 h, for example, can result in large inaccuracies. If the GFR is to be useful to the clinician in following a patient's progress, in some cases over many years, it is important to use a method which is less prone to inaccuracy (arising from mere forgetfulness) and generally more repeatable.

Our standard method requires two GFR blood samples (at 2 and 4 h), thus enabling a proper slope clearance determination. Minor timing inaccuracies are then of considerably less importance and there is an overall confidence which has never quite been achieved with the single 3-h sample method.

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Constable, A. R., Hussein, M. M., Albrecht, M. P., Thompson, F. D., Philalithis, P. E. and Joekes, A. M. (1979). Single sample estimates of renal clearances. *British Journal of Urology*, **51**, 84-87.

Requests for reprints to: A. R. Constable, Honorary Senior Lecturer in Medical Physics, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Case Reports

Repeated Pregnancies Following *in vitro* Fertilisation Therapy in Cases of Male Infertility

J. HEWITT and J. COHEN, *Bourn Hall Clinic, Bourn, Cambridge*

In couples with a long history of infertility due to a male factor only, the incidence of clinical pregnancies following one treatment cycle of *in vitro* fertilisation (IVF) therapy is comparable with the pregnancy rate for couples whose infertility is due to tubal factors alone (Cohen *et al.*, 1984; Edwards *et al.*, 1984). The potential of IVF therapy for male infertility is demonstrated here by the establishment of repeated pregnancy following two separate treatment cycles for two such couples.

Case Reports

Case 1 This couple was referred with a 5-year history of primary infertility due to extreme oligoasthenospermia secondary to delayed descent of both testicles in adolescence. Treatment with anti-oestrogens and steroids had failed to improve the situation and following two unsuccessful attempts of bi-daily intrauterine artificial inseminations with the husband's washed semen, IVF therapy was commenced. Three IVF treatment cycles have been completed (with respectively 1, 3 and 5 mature oocytes being recovered), producing one normal live male infant following the first treatment cycle, and one singleton ongoing pregnancy following the third treatment cycle 2 years later. This pregnancy has been confirmed by uterine ultrasonography and rising human chorionic gonadotrophin levels. In all three treatment cycles, the motile sperm concentration was less than 0.5×10^6/ml (Table). In the third treatment cycle, since fertilisation had not occurred by the day following the original insemination, a second, freshly produced semen specimen was required in order to achieve delayed fertilisation and subsequent pregnancy.

Case 2 This couple, with a 7-year history of primary infertility due to asthenospermia, also underwent three IVF treatment cycles, producing 1, 2 and 6 mature oocytes respectively. On the first occasion fertilisation did not occur, probably due to the low number of oocytes recovered. The second treatment cycle resulted in the delivery of a healthy male infant and a further ongoing pregnancy has been established following the third treatment cycle. On all three occasions the semen specimens showed a normal count, but the motility of spermatozoa was always less than 20%, with only very weak forward progression (Table). On each occasion two separate semen specimens were collected in the form of split ejaculates into a mixture of 50% wife's serum: 50% culture medium. After centrifugation the semen pellets were resuspended in culture medium and left at room temperature under paraffin oil for several hours to remove immotile spermatozoa, spermatozoal clumps and cellular debris. After careful removal of the relatively "motile sperm rich" upper portion of each of the resulting two solutions, the one with the higher concentration of motile spermatozoa was used for insemination, with the remaining sperm suspension being stored at room temperature and used for repeated inseminations as necessary.

Comment

It has been shown that through careful collection and preparation of semen specimens, in combination with IVF therapy, couples with exclusively male infertility can be offered a 23% pregnancy rate per cycle (Cohen *et al.*, 1984). The prospects of achieving pregnancy by conventional methods in such cases are extremely low. We have attempted intrauterine insemination with washed husband's semen in many patients with a long history of male infertility in whom conventional treatment had previously been unsuccessful. The pregnancy rate per cycle in such cases was less than 5%.

Table Semen Parameters and Results of IVF

Patient	*Treatment cycle*	*Concentration of spermatozoa* ($\times 10^6$/ml)	*Percentage motile*	*Proportion of oocytes fertilised*	*Outcome of treatment*
1	1	1	25	1/1	One child delivered
	2	0.4	40	3/3	Not pregnant
	3	0.5	25	2/5	Ongoing pregnancy
2	1	36	20	0/1	—
	2	42	5	2/2	One child delivered
	3	50	10	3/6	Ongoing pregnancy

The success or failure of IVF therapy in the treatment of male infertility is dependent on a combination of factors. Sufficient numbers of mature oocytes per case must be recovered and a flexible approach to the variety of semen preparation and insemination techniques available must be maintained. Each treatment cycle requires a different approach and there is no single IVF protocol which can be successfully applied to all cases of male infertility.

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Requests for reprints to: J. Hewitt, Bourn Hall Clinic, Bourn, Cambridge CB3 7TR.

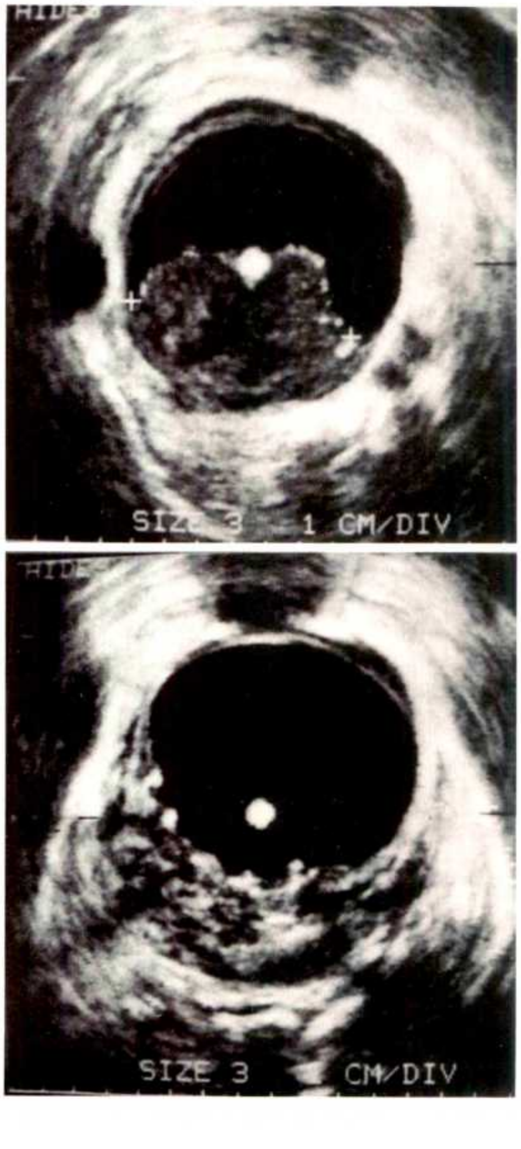
Problem of Extravasation of Irrigating Medium Following Transurethral Resection of Bladder Tumours

M. FOX, *Department of Urology, Royal Hallamshire Hospital, Sheffield*

One of the complications of transurethral resection of the prostate gland is the dilutional hyponatraemic and haemolysis syndrome, particularly when water is used as the irrigating medium (Creevy and Reiser, 1963). The relatively easy flow of fluid into opened, mainly capsular veins is described as the reason for the phenomenon (Blandy, 1978). Transurethral resection of bladder tumours, particularly large ones, can also produce marked extravasation which can be shown clearly by intravesical ultrasound examination. The extravasated fluid may subsequently be absorbed into the general circulation. Resection of extensive bladder tumours requires careful observation post-operatively for the post-transurethral resection syndrome, particularly as water continues to be used (probably unnecessarily) by many urologists.

Case Report

A 91-year-old female with a large bladder tumour was cystoscoped under general anaesthesia and the presence of a 6 × 8 × 8 cm sessile, well fronded neoplasm occupying most of the right posterolateral aspect of the bladder was confirmed and then demonstrated with an intravesical ultrasound probe (Brüel and Kjaer, Type 3409) (Fig. 1 Top). The bladder wall was intact with no evidence of muscle involvement. This was later confirmed histologically and the tumour was found to be a well differentiated transitional cell carcinoma. After transurethral resection the ultrasound examination was repeated. The contour of the bladder is irregular because resection was carried into the superficial bladder muscle. The muscle echoes in that region appear separated throughout the thickness of the wall and the lucent zones, which represent the irrigating fluid, extend deeply into the perivesical tissues (Fig. 1 Bottom).



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Requests for reprints to: M. Fox, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

Round Headed Sperm

P. D. SUTHERLAND, G. V. LANDON, P. L. MATSON and J. P. PRYOR, *St Peter's Hospitals and King's College Hospital, London*

Round headed sperm are a rare cause of male infertility and their abnormal appearance is due to lack of the acrosome. This structure is thought to be necessary for ovum penetration but there are species differences in acrosome function and its precise role in human fertilisation is still not clearly established (Pedersen and Fawcett, 1976).

Case Report

A 35-year-old male presented with a 7-year history of primary infertility. There were no causative factors in his history and on examination he was a normal healthy male. Serum levels of LH, FSH and testosterone were normal and there was no evidence of circulating antisperm agglutinins. Semen analysis showed a volume of 2.3 ml with a sperm concentration of 103 million/ml. Sperm motility was 50% but morphological examination revealed only round headed sperm. Electron microscopy confirmed the complete absence of the acrosome (Fig.) in all spermatozoa. The heterologous ovum penetration test, carried out as described by Tyler *et al.* (1981), showed zero sperm attachment and penetration of the 26 eggs tested.

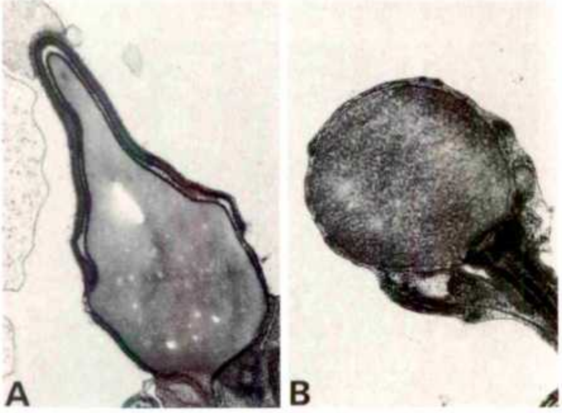

Fig. Electron microscopic appearances of (A) normal spermatozoal head and (B) abnormal round spermatozoal head lacking acrosome. (Magnification × 20,400).

Comment

Round headed sperm were described as a rare cause of infertility and their electron microscopic features noted by Hostein *et al.* (1973). The heterologous ovum penetration test allowed for *in vitro* assessment of the functional ability of the round headed spermatozoa to attach to and penetrate ova. This is the first report of a functional assessment of round headed sperm using this test. The poor result supports the proposition that the acrosome is needed for ovum attachment and penetration by human spermatozoa.

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Requests for reprints to: P. D. Sutherland, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

Distalgesic Abuse and Retroperitoneal Fibrosis

J. A. J. H. CRITCHLEY, M. F. SMITH and L. F. PRESCOTT, *Departments of Clinical Pharmacology and Urology, Royal Infirmary, Edinburgh*

Case Report

A previously healthy 58-year-old clerk, on no drug therapy, was prescribed Distalgesic (paracetamol plus d-propoxyphene) for abdominal shingles. He took over 16 tablets daily for 6 months despite troublesome constipation and thereafter about 10 tablets daily for 4 months, when he presented with mild angina, intermittent right-sided abdominal pain and low backache. He was hypertensive (190/100 mm Hg), had right loin tenderness and microscopic haematuria. Haemoglobin was 10.9 g/dl and ESR 115 mm/h. Plasma urea and creatinine were 17 and 0.34 mmol/l respectively. An intravenous urogram and subsequent retrograde pyelogram demonstrated bilateral hydronephrosis with localised obstruction of both ureters at the fourth/fifth lumbar vertebral level, but without medial deviation.

Laparotomy revealed a fibrous retroperitoneal mass from which the ureters were mobilised and then wrapped in omentum. The bowel was normal. Histological examination showed typical retroperitoneal fibrosis. The patient made an excellent recovery and has remained well for over 6 years. Intravenous urograms and plasma urea and creatinine concentrations were normal at 6 months, 2 and 5 years.

Comment

As with previous reports relating retroperitoneal fibrosis to drug therapy, the association with Distalgesic in this case can only be circumstantial. The presentation and radiological features of narrowing of the middle third of the ureter without medial deviation are similar to those in other reports involving analgesic abuse (MacGregor *et al.*, 1973; Lewis *et al.*, 1975). The mechanisms of drug-induced retroperitoneal fibrosis are unknown, but a vascular basis has been proposed and hence the microangiopathy affecting the renal pelvis, ureter and bladder in analgesic abuse (Abrahams *et al.*, 1976) may be relevant. Retroperitoneal fibrosis has been associated with methysergide, but its role could be questioned since in patients with migraine severe enough to require its use heavy analgesic consumption is inevitable.

The dextropropoxyphene in Distalgesic is a narcotic analgesic capable of inducing dependence and it is probably more likely to be abused than other combination analgesics linked with retroperitoneal fibrosis (MacGregor *et al.*, 1973; Lewis *et al.*, 1975). As in this case, such patients may be unwilling to divulge the true extent of their analgesic abuse and the role of these drugs in the aetiology of retroperitoneal fibrosis and ureteric stricture may easily be overlooked.

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Requests for reprints to: J. A. J. H. Critchley, Department of Clinical Pharmacology, Royal Infirmary, Edinburgh EH3 9YW.

Carcinoma in a Post-diversionary Bladder

D. TURINI, A. TRIPPITELLI and P. PROSI, *Department of Urology, University of Florence, Florence, Italy*

The twelfth case of carcinoma developing in the post-diversionary bladder is reported and pertinent literature is reviewed. All except two tumours became apparent within a short time. The relationship between chronic bladder inflammation, metaplastic changes and carcinoma is noted. Simple cystectomy at the time of diversion seems advantageous.

Case Report

A 59-year-old female underwent hysterectomy in 1961. The right kidney was removed later because of hydropyonephrosis and in 1976 hydronephrosis of the left kidney necessitated a permanent nephrostomy.

In 1981 the patient presented with discharge and bleeding from the defunctioned bladder, and fever. Cystoscopy revealed a reduced bladder capacity and biopsy showed transitional carcinoma with areas of squamous metaplasia. Total cystectomy was performed and histological findings confirmed the previous biopsy. Convalescence was uneventful.

Comment

The relationship between long-standing inflammation, metaplastic changes and bladder carcinoma cannot be ignored. In 11 previously reported patients with carcinoma in defunctioned bladders, 8 had suffered bladder infection, 3 had squamous metaplasia, 2 had cystitis cystica and 1 had interstitial cystitis (O'Flynn and Mullaney, 1974; Garvin *et al.*, 1977; Aaronson, 1978).

One must emphasise the need of careful follow-up of defunctioned bladders by means of cytological examination, cystoscopy, biopsy and the

SCRA test. Finally, we agree with other authors that simple cystectomy at the time of permanent diversion seems advantageous.

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O'Flynn, J. D. and Mullaney, J. (1974). Vesical leukoplakia progressing to carcinoma. *British Journal of Urology*, **46**, 31-37.

Requests for reprints to: A. Trippitelli, Department of Urology, University of Florence, Viale Pieraccini, 18, 50139 Florence, Italy.

Point of Technique

Use of the Metal Stylet of a Ureteric Catheter for Ureteric Meatotomy

R. P. YAXLEY, *131 Wickham Terrace, Brisbane, Queensland, Australia 4000*

One of the simplest and most readily available instruments for ureteric meatotomy is a ureteric catheter with a steel stylet combined with the cutting current from a diathermy machine.

The patient is prepared and draped for cystoscopy. The steel stylet is removed from the sterile ureteric catheter and the distal 2 inches cut off. The stylet is then reintroduced so that ½ inch can be projected beyond the end of the catheter while 1 inch or more still projects at the operator's end. The stylet is then withdrawn within the catheter.

The cystoscope is passed and the ureteric catheter is introduced. As soon as it is visible in the field of view the steel stylet is projected ¼ inch beyond the end of the catheter. The catheter with the projecting stylet is then advanced until the stylet enters the stenosed ureteric orifice. When the cystoscope is elevated away from the ureteric orifice, Albarran's lever is relaxed and the stylet tents the ureterocele. The cutting diathermy is applied to the operator's end via the diathermy lead and pencil, whereupon the stylet zips through the ureterocele. The size of the hole is determined by the operator, as is the distance the stylet projects beyond the ureteric catheter. Impacted stones can also be released in this manner. The opened ureteric orifice seems to heal to a normal functioning opening and reflux does not result.

The procedure is simple, cheap and universally available.

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Notices

Edinburgh Urological Festival

Edinburgh. 28-30 August 1985

The Urological Festival is a post-graduate course of lectures by invited speakers and short papers by participants.

The main topics for the 1985 meeting include reconstructive urological surgery, psychosexual medicine, computers in urology, endo-urology and recent advances in chemotherapy.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Urological Research Meeting

Guy's Hospital, London. 10 January 1986

The meeting will provide a forum for the informal presentation and discussion of completed work and work in progress with invited participants from the related basic sciences such as smooth muscle physiology and pharmacology, oncology, anatomy and nephrology.

Further particulars from: Mr A. R. Mundy, Department of Urology, Guy's Hospital Medical School, London Bridge, London SE1 9RT. Please state if you wish to present a paper.

Aluminium in Renal Disease

University of Surrey, Guildford. 16-18 September 1985

An international conference to highlight recent knowledge of the problems with aluminium and other metals in the management of renal failure.

Further information from: Mrs Janet Williams, Robens Institute, University of Surrey, Guildford GU2 5XH.

European Nuclear Medicine Congress 1985

London. 3-6 September 1985

Further particulars from: Congress Secretariat, Institute of Nuclear Medicine, Middlesex Hospital, Medical School, Mortimer Street, London W1N 8AA.

12th Meeting of the International Study Group for Steroid Hormones

Rome, Italy. December 1985

The main topics of the meeting will be:

1. Steroid peptide interaction
2. Sex hormone antagonists.
3. Intratissular steroids and hormone dependent corneu.

Deadline for presentation of abstracts: 30th June 1985.

Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma, viale del Policlinico, 00161 Rome, Italy.

Fifth International Symposium of Operative Andrology: Erection

Berlin, Germany. 15 March 1986

Further particulars from: A. Kelami, Department of Urology, Klinikum Steglitz, Free University of Berlin, Hindenburgdamm 30, D-1000 Berlin 45, F. R. Germany, or J. P. Pryor, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

Sixth International Symposium on Radionuclides in Nephro-urology

Lausanne, Switzerland. 5-7 May 1986

Topics: Radionuclides and complementary/competitive methods in the investigation of kidneys, urinary tracts and relative bone disease. Basic and clinical sciences.

Deadline for submission of abstracts: 16 December 1985.

Further particulars from: A. Bischof-Delaloye, Division Autonome de Médecine Nucléaire, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland.

Seventh Congress of European Association of Urology

Berlin, Germany. 15 March 1986

Further particulars from: Professor F. Balogh, Department of Urology, Semmelweis University of Medicine, Maria U. 39, 1085 Budapest VIII, Hungary.

British Journal of Urology (1985), **57**, 490

Book Reviews

IgA Mesangial Nephropathy. Contributions to Nephrology. Volume 40. Edited by G. D'Amico, L. Minetti and C. Ponticelli. Pp. viii+308. Basel: Karger. 1984. Price SFr. 163.–; DM 195.–; US$97.75.

This edition of Contributions to Nephrology is a reminder to urologists that IgA mesangial nephropathy should be considered as a possible diagnosis in any patient, particularly younger patients, presenting with persisting or recurrent macroscopic or microscopic haematuria. Since the first description of this condition by Berger in 1968, this form of glomerulonephritis has been increasingly recognised and occurs in 10 to 30% of all patients with primary glomerulonephritis. The condition is most commonly idiopathic but may also be a feature of Henoch-Schönlein purpura, and, in addition, may be associated with systemic disease, particularly cirrhosis of the liver. While generally benign, in a small proportion of such patients progressive renal impairment may develop.

This book is a comprehensive account of this condition with contributions by many recognised experts in this condition. While it is unlikely that urologists will find all of this book of value, the clinical accounts of this condition may either be of interest or of reference value to them.

Ultrasound in Urology. Second edition. Edited by M. I. Resnick and R. C. Sanders. Pp. xii+430. Baltimore/London: Williams and Wilkins. 1984. Price £48.00.

In their preface to the second edition of this comprehensive text the editors acknowledge that ultrasonic techniques and applications have advanced considerably since the publication of the first edition some 5 years ago. In recognition of this fact, many of the chapters have been rewritten by current experts in their individual fields and completely new chapters have been added. Despite this the book remains of manageable size, having been lengthened by only 50 pages. Indeed, in 1984 it could be argued that in a text such as this the section covering the history of ultrasound may well have been left out altogether. On the other hand, a new section discussing current instrumentation provides a valuable insight into the great advantages offered by "real time" in its various shapes and forms.

The chapter dealing with neoplasms and pseudotumours has been completely rewritten and includes extensive references. The investigation of acute renal failure is deservedly allocated a whole new chapter, while retroperitoneal problems and scrotal and adrenal ultrasound have been substantially updated. During the last 4 years, applications of ultrasound in the lower urinary tract have burgeoned and this is reflected in separate detailed chapters covering the bladder, the prostate gland and the potentially important area of urodynamics.

The text is generously complemented by ultrasound images which are of considerable value but variable quality. The second edition of this book gives the urologist an excellent and broad coverage of the current scope of ultrasound in his field; at £48 in the United Kingdom it provides excellent value for money and should grace the library shelves of any specialist department of urology.

1983 Year Book of Urology. Edited by J. Y. Gillenwater and S. S. Howards. Pp. 360. Chicago, London: Year Book Medical Publishers. 1983. Price £32.00.

The Year Book Series continues to provide a distillation of the main American and international biomedical journals. For this volume 3500 articles and 58 journals were reviewed and 250 articles summarised for this publication. The format is very easy to read and the short editorial comments after each summary help to emphasise the relevance of the article. The excellent 6-page introduction puts these summaries in perspective and highlights the main contributions to the urological literature in 1982. Each Year Book represents a vast amount of work by the editors, who must continue to rely on their book being bought by those readers who never find time to scan the main journals. These books are still the easiest and most convenient way to obtain an update on the whole field of urology. Highly recommended.

Intra-renal Surgery. Edited by J. E. A. Wickham. Pp. x+323. Edinburgh: Churchill Livingstone. 1984. Price £27.00.

The editor and 22 distinguished contributors, each an acknowledged expert in his field, bring together in this one volume an excellent and well illustrated account of recently developed techniques in operative renal surgery. The techniques described include ischaemic renal surgery and its effect upon renal function, intrasinusal surgery, coagulum pyelolithotomy, nephrotomy, extracorporeal renal surgery, transarterial occlusion and embolisation, and contact-free fragmentation of kidney stones using shock waves, which seems destined to change the working practices of all urologists.

The book derives from the meetings of the members of the European Intra-renal Surgical Society over the past 6 years and shows how fruitful such meetings have been. It is essential reading for all practising and training urologists.

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VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

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Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

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Contraindications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of VICRYL (Polyglactin 910) and Coated VICRYL Sutures in neural tissue and in cardiovascular tissue have not been established.

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Package Quantities Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

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450 Hyponatraemia Following Transurethral Resection of the Prostate
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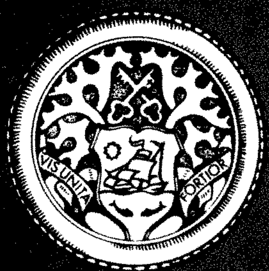

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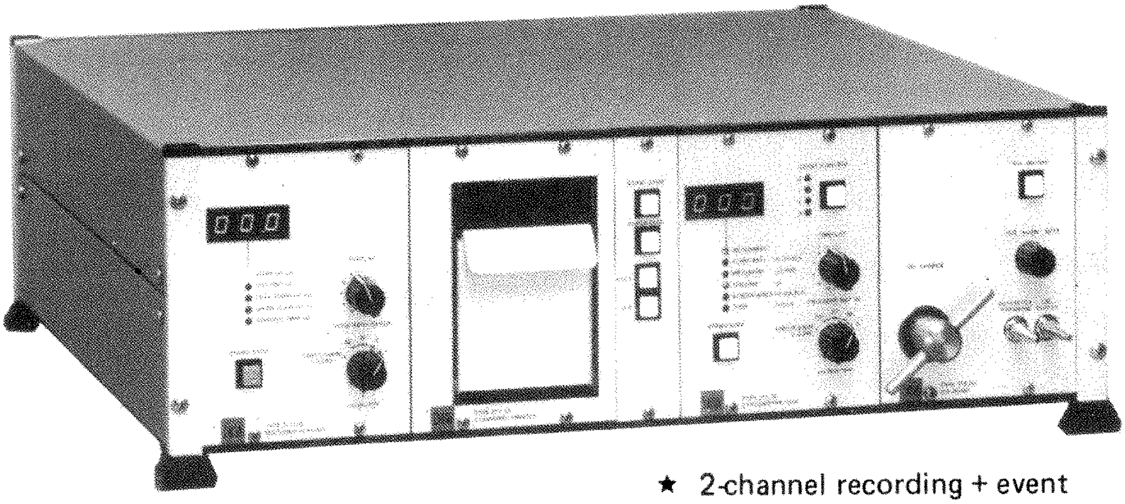

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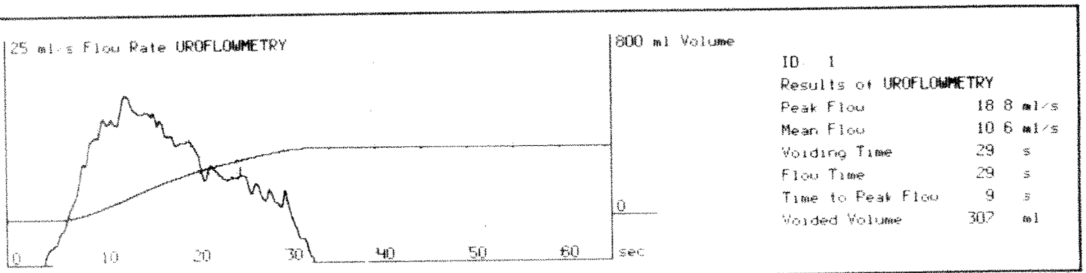

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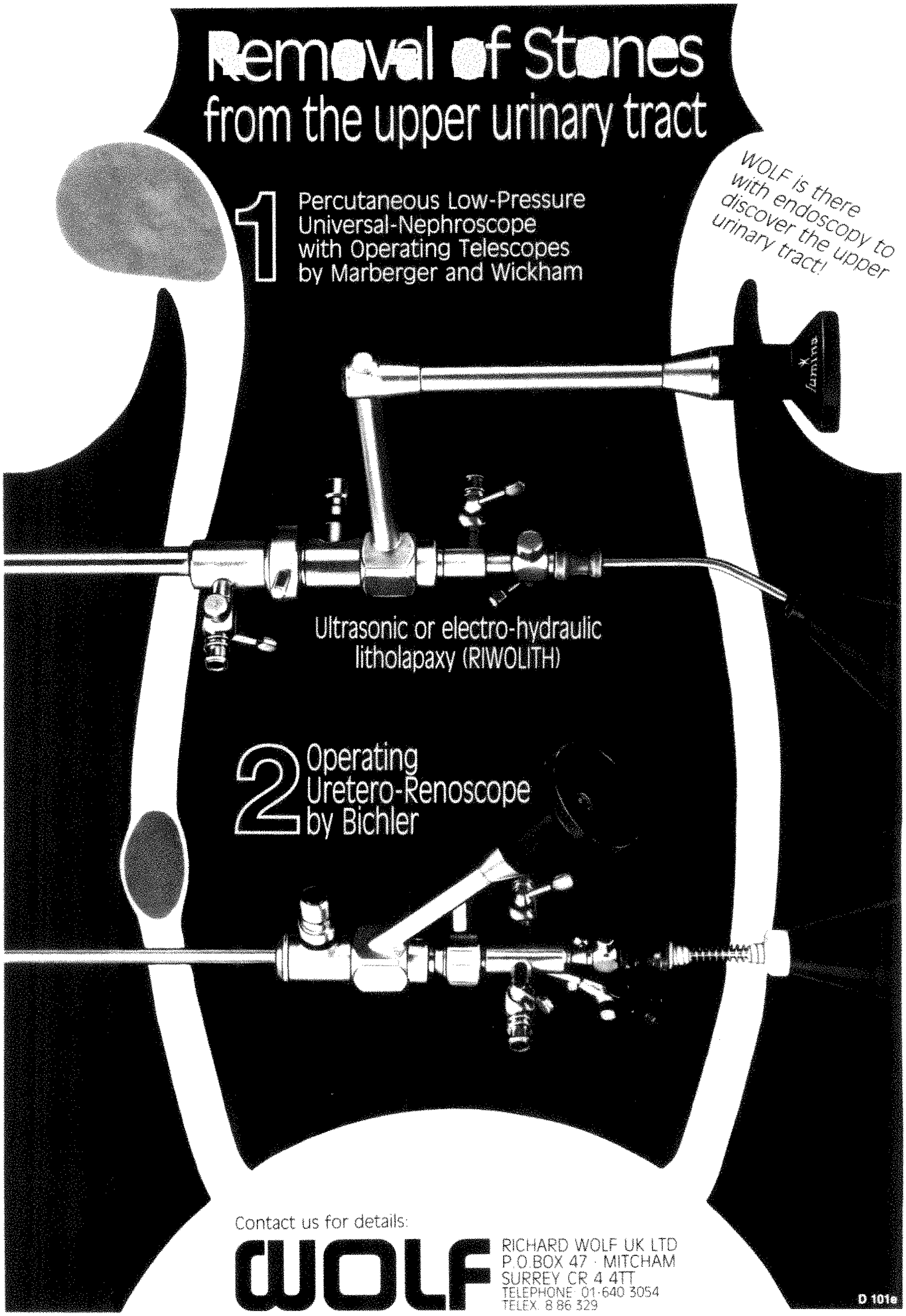

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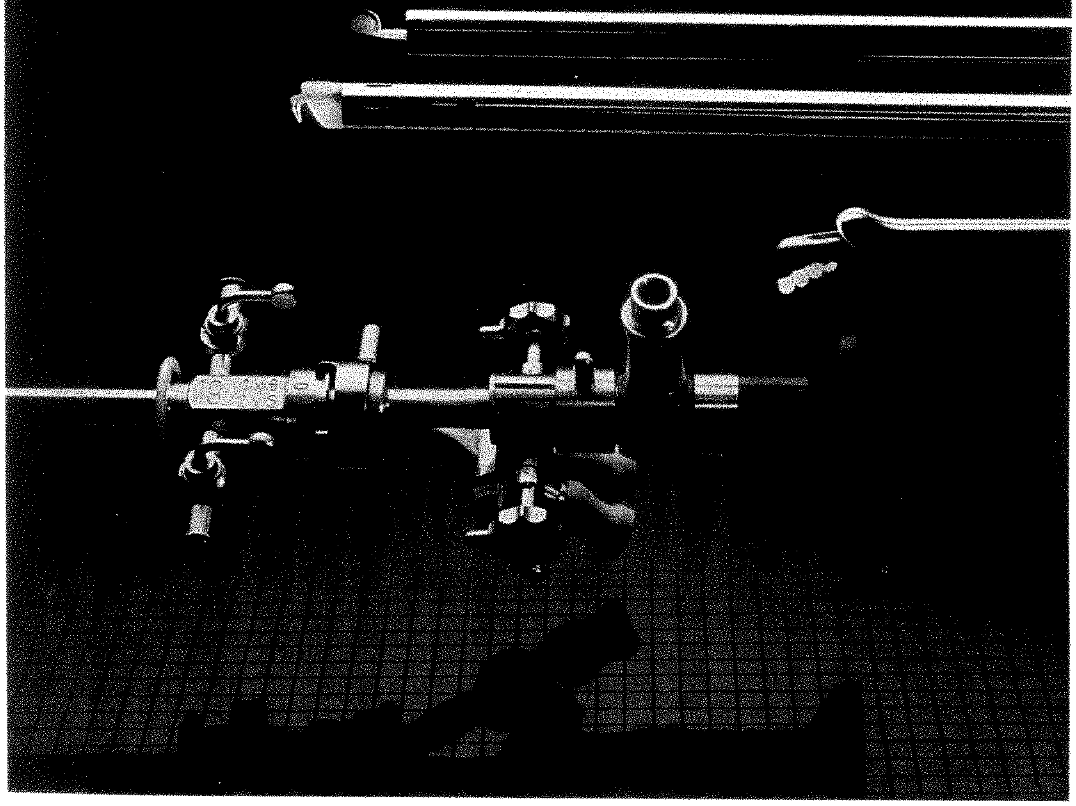

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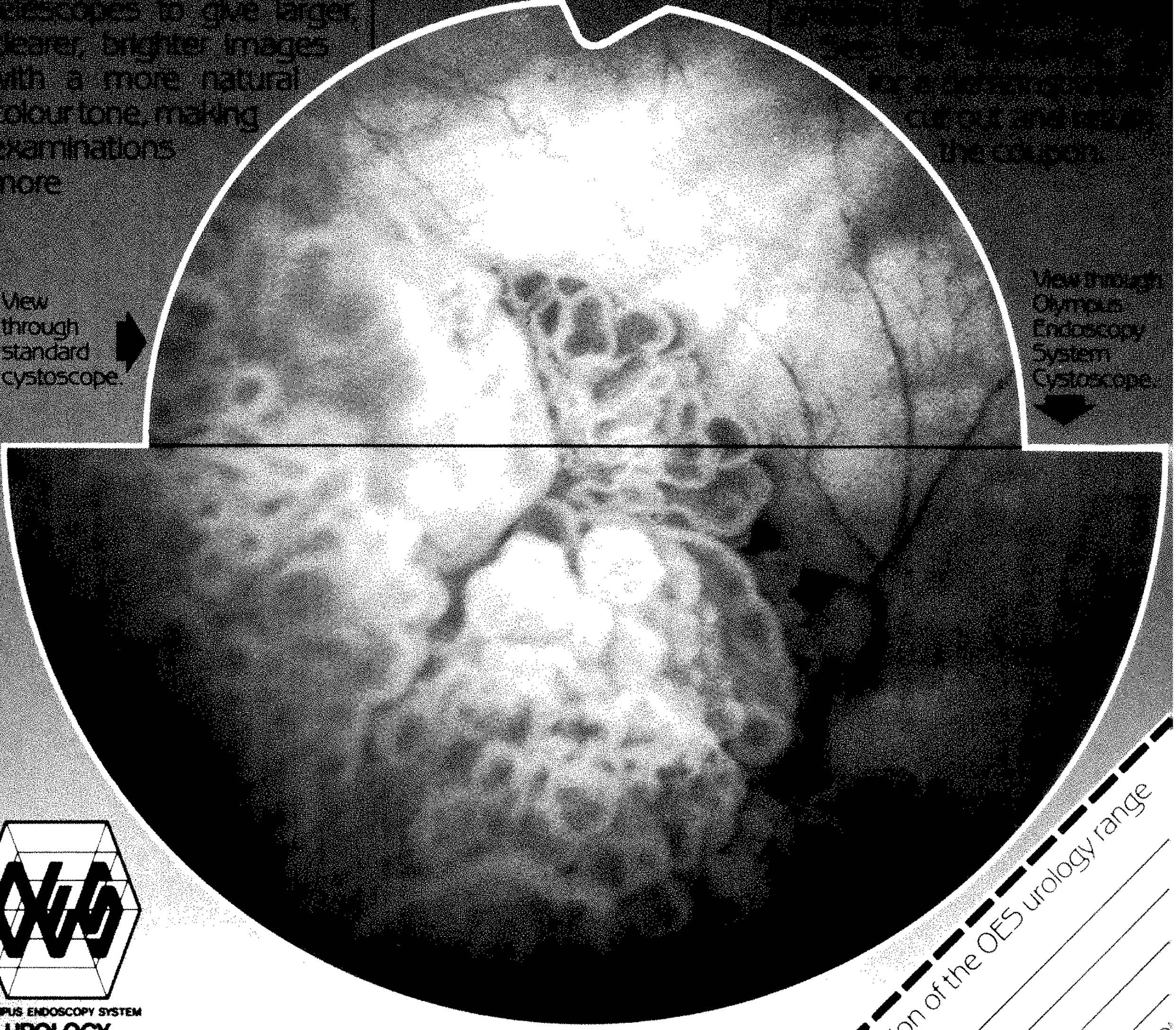
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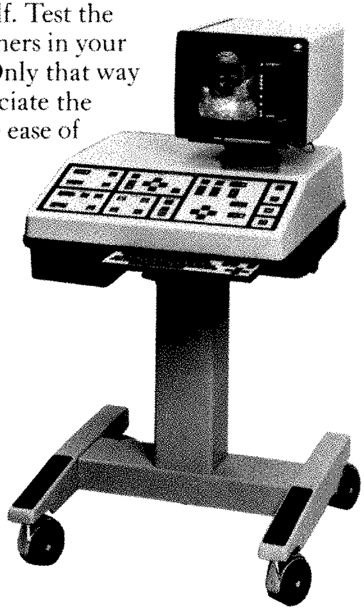

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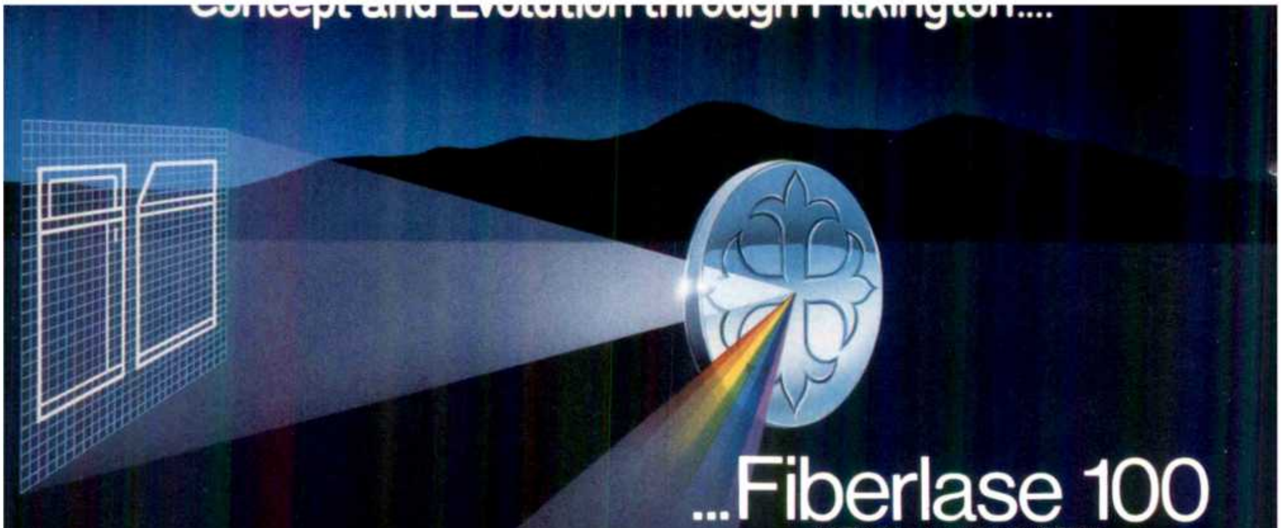

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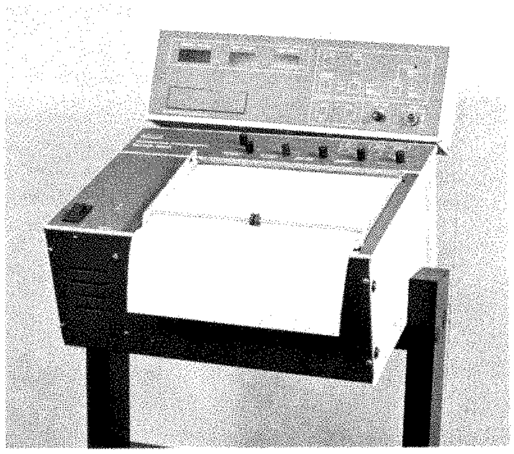

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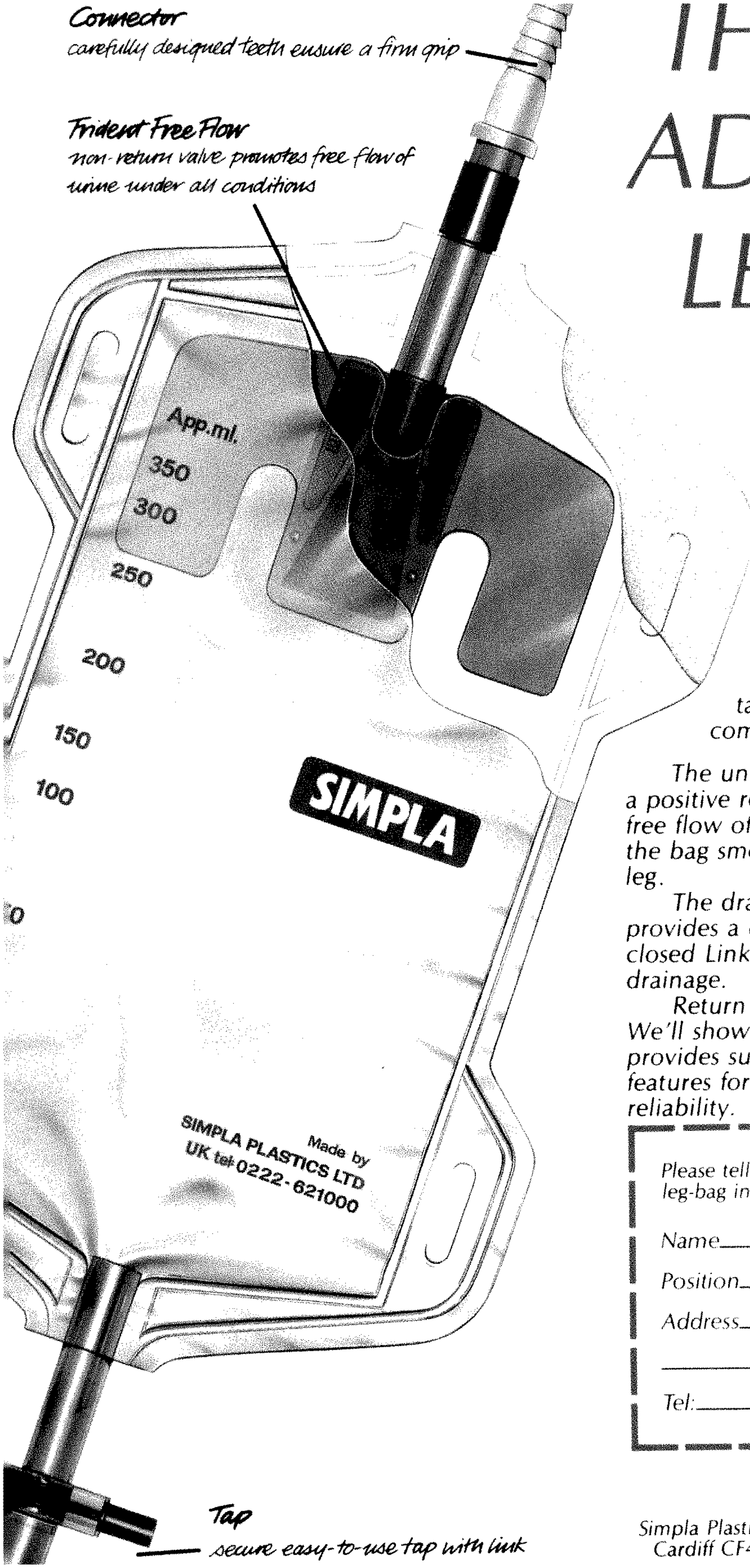
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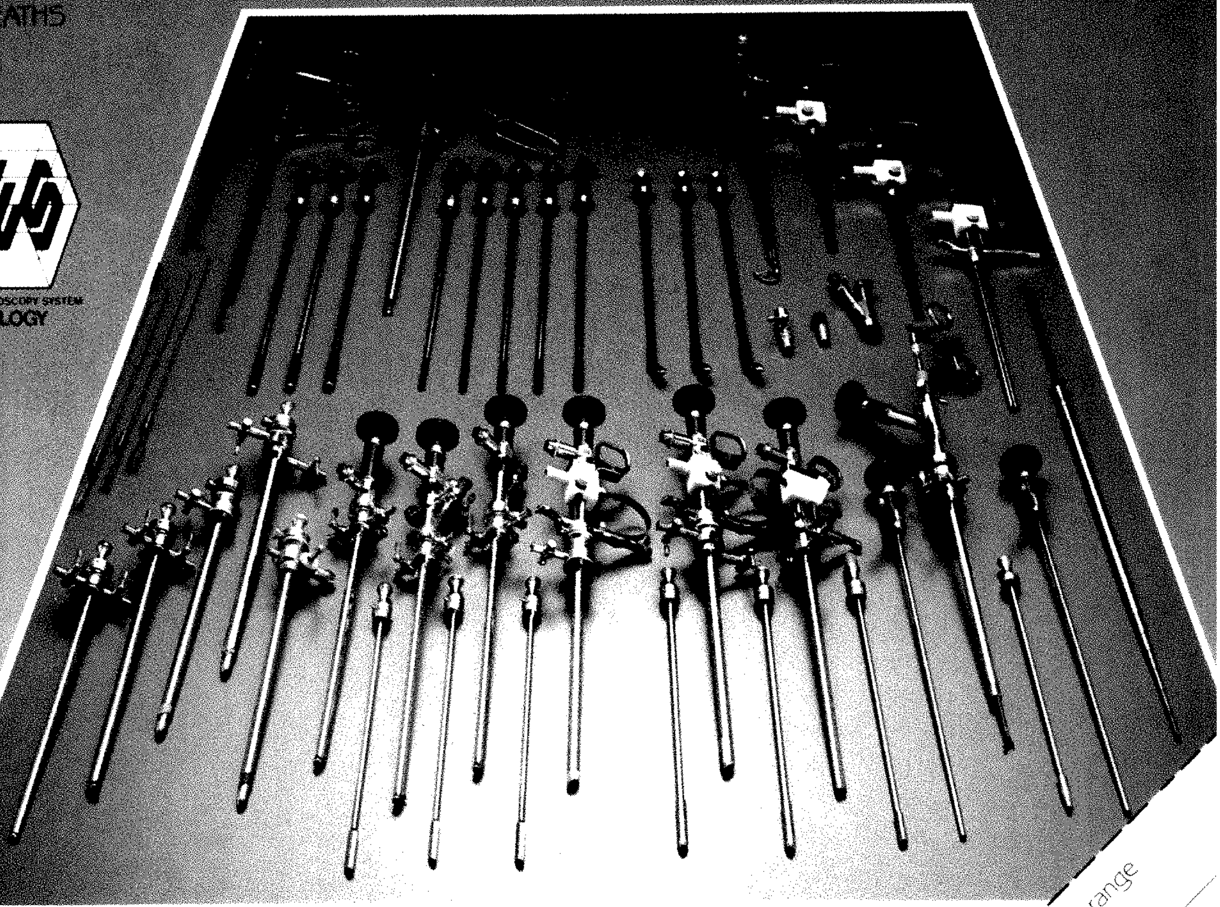

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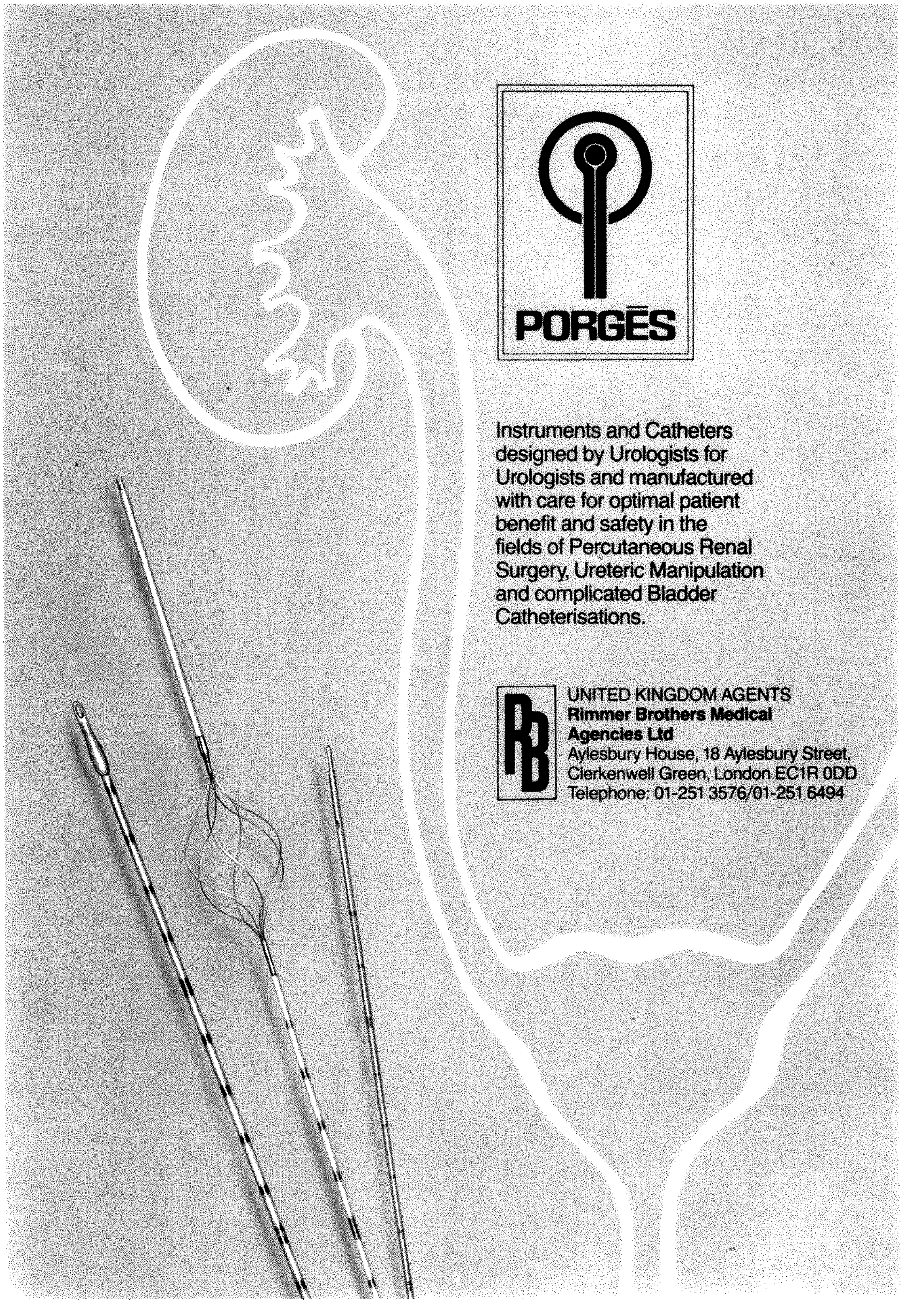

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REVIEW

Epidemiology of Stone Disease

R. SCOTT

Department of Urology, Royal Infirmary, Glasgow

It is perhaps surprising that despite sophisticated modern technology, basic information about the pattern of disease in communities is remarkably little understood. The concept of examining a community on a random basis in order to determine the pattern of a particular disease and subsequently to repeat the exercise to determine the changing rate of the particular disease process has rarely been attempted. In most countries the information available on renal stone epidemiology is based on an analysis of significant cases which present at a hospital (Andersen, 1968). The number of cases actually present in a community may be very different from those which present clinically.

This review summarises the major surveys undertaken in recent times in several different countries.

USA

There have been three major reports since 1950 and the authors freely admit that the information presented is deficient. Of the hospitals surveyed between 1948 and 1952 only 138 supplied information which was complete enough to be analysed (Boyce *et al.*, 1956) and in the survey of 1974 only 278 institutions could be analysed (Sierakowski *et al.*, 1978). A similar criticism can be levied at the study of Burkland and Rosenberg (1955) and the earlier work of Holmes and Caplan (1930).

If we assume that the data collected were uniform throughout the study by Boyce *et al.* (1956), then there are some interesting data regarding the different rates of stone disease between states in the USA (Table).

Table Stone Incidence in Four States in the USA

State	*Rate per 10,000 admissions*
South Carolina	19.25
Georgia	18.42
Wyoming	5.81
Missouri	4.31

Burkland and Rosenberg (1955) also appear to confirm a higher "incidence" in southern and south-eastern states and observed that the recurrence rate was highest in those areas where the disease was more prevalent.

Studies carried out before 1950 revealed that the rate of stone disease as shown by actuarial statistics was 23.9 per million in Utah compared with 2.4 per million in Vermont in 1937 (Vermooten, 1937), demonstrating that state differences have been recognised for 50 years.

Most of these studies were orientated towards or sought to answer questions relating to such factors as race, diet, climate and other geographical factors. As early as 1935, Reaser noted that stone disease was a rare occurrence in the southern states in the negro population. A study of this particular work raises an important point, *viz.* the author makes no reference to the availability and rate of admission to hospital facilities for the negro population in the southern states.

In a study in Virginia in 1946, Dodson and Clark noted that of 4524 stone subjects less than half (1800) were negroes.

Studies on the incidence of stone disease in the US armed forces, which might be regarded as having a more even socio-economic pattern, confirmed a difference between whites and blacks in that the

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rate of stone problems was 60 to 1 respectively (Pierce and Bloom, 1945).

Racial groups within America have been studied in units of less than State size. One such investigation in San Francisco revealed that the Chinese population was twice as likely to develop stone disease as the whole population and that Asians in Hawaii had a stone disease rate of 27% compared with 2.7% in a corresponding white population (Fay, 1981).

What is of particular and practical importance is the realisation that more than 1 person per 1000 suffers from stone disease in the US compared with 0.2 to 0.5 per 1000 in Mediterranean countries (Malek, 1977).

Northern Europe

There have been many studies on urinary tract stone disease in Sweden, Finland, Norway and Denmark (Hellstrom 1949; Sallinen, 1959; Ahlgren and Lorstad, 1965a and b). In these early studies it was considered that there was a rising incidence of stone disease and in 1975 a retrospective investigation by Ljunghall and Hedstrand considered the problem in men aged between 49 and 50 who were living in an urban environment. This, coupled with a study of hospital admission rates, suggested an increasing incidence of upper tract stone disease.

Both Grossman (1938) and Hellstrom (1949) noted a rise in stone disease in Sweden after the 1914/1918 war. This has been known for some time and has given rise to speculation that the increase could be related to dietary changes brought about by the widespread food restrictions in Western Europe during the war. Sweden was neutral and therefore may have been less implicated in reduced agricultural production, unless as a secondary effect. In Finland, Sallinen (1959) found no difference between urban and rural dwellers with respect to stone disease.

Ahlgren and Lorstad (1965a and b) reported that between the sexes two peaks of increased incidence occurred, with no seasonal variation.

From Norway there was a very full review of the problem by Andersen (1966), who found a general fall in the incidence of bladder stones and an apparent increase in upper tract stone disease during the period of study. The last of the Scandinavian studies was that of Larsen and Phillip in 1962; they considered the problem within the medical profession in Denmark and considered it to be of major significance.

Another study from the Scandinavian countries by Almby *et al.* (1975) showed that within a specific geographical area the incidence of stone disease did not significantly change from a rate of 180 per 100,000 inhabitants between two points in time 30 years apart. The authors drew attention to deficiencies in earlier studies. By contrast, Norlin *et al.* (1976), in a well controlled study, found an apparent increase in stone incidence in a Swedish urban district—the time periods being 1938 to 1955 and 1968 to 1970—where it was observed that the male rate rose from 2.2 to 3.3% and the female rate from 0.5 to 0.8%.

In recent reviews of the problem in Sweden it was observed that hospital statistics may well underestimate the prevalence of stone disease, that the lifetime risk varies between 10 and 20% for males and 3 and 5% for females and that the disease may be tending to affect younger persons in the country (Ljunghall *et al.*, 1981).

Western Europe

United Kingdom

One of the earliest studies in this field came from Scotland (Anderson, 1974). It was based on the hospital admission rates in one small community of 20,000 inhabitants living on Harris/Lewis, off the Scottish coast, and gave a rate of 68 per 100,000 admissions.

Subsequent investigations by Scott *et al.* (1977, 1978) showed that the prevalence of stone disease in a randomly selected group within the population was 3.47%. In the medical profession the incidence of symptomatic stone disease was as high as 17% in surgeons (Scott, 1971). In England and Wales, *i.e.* the southernmost countries in the UK, there have been few epidemiological studies of stone disease. Barker and Donnan (1978) found a higher rate in the southern parts of these two countries.

Rose and Westbury (1975) noted a diametrically different pattern, *i.e.* in Scotland and northern England the incidence was higher than in southern England. In a specific study of the calcium content of tap water no obvious correlation was found between water hardness and stone incidence (Donaldson *et al.*, 1979). Blacklock (1969) studied the pattern of urolithiasis in the Royal Navy and noted a difference between occupations within this closed and highly selected community.

Germany

Recent work in the German Federal Republic is based on two main studies.

(1) Of 4015 individuals who were asked to respond to a simple questionnaire, 202 reported one or more episodes of stone disease (Hesse *et al.*, 1981).

(2) A nationwide survey of the incidence (0.5%) and prevalence (4%) of the disease was carried out by the same authors. They studied occupational factors and emphasised that people in rural areas were less likely to be affected than city dwellers (Vahlensieck *et al.*, 1982).

Eastern Europe

Czechoslovakia

In this country the population tends to be distributed in such a way that there is a "concentration of people of various occupations" (Mates, 1969). The author found that the lowest rate of stone incidence occurred in certain border areas where there was a large agricultural element. Like Blacklock (1969), he found that people in sedentary occupations were more likely to develop stone disease than those involved in more active work.

Austria

Zechner and Scheiber (1981) studied the effects of social conditions on the likelihood of recurrent disease. They concluded that nutritional factors were important in stone epidemiology, as were rapidly changing lifestyles. They suggested specifically that increased spending on food resulted in a rise in the recurrence rate.

Middle East

In an area where the climate tends to be dry and arid it is hardly surprising that several studies have emanated from these countries.

Israel

Of particular interest in this country is the fact that the inhabitants have emigrated from a wide variety of locations. In addition, they are all of the same race and an increase in the population has caused changes in the economy within the relatively short space of 35 years.

One of the original observations from Israel suggested that the failure to increase fluid intake while undertaking heavy manual work in hot climatic conditions resulted in a reduced output of urine with concomitant concentration and eventual crystallisation (Frank *et al.*, 1959). The figures produced, giving a rate of symptomatic stone disease of 1.18%, do not suggest an incidence which is materially different from that noted by other workers and since it is symptomatic disease which is being considered, the true rate may not be apparent. However, it was decided to encourage the population to increase their fluid intake. Frank *et al.* (1966) also commented upon the high incidence in northern and central Israel and in the southern part of the country. The rate of stone episodes in the population given advice was 0.28% compared with 0.85% in "control" villagers who were not encouraged to increase their fluid intake (Frank *et al.*, 1966).

Jews born in Israel have a lower rate of calcium oxalate stone disease than incomers, but uric acid stones are more likely to occur in native born Jews (Zaidman and Pinto, 1976). This supports the concept of local factors, such as diet, being important.

Jordan

A study from Jordan which concentrated on hospital admission rates during a 4-year period revealed that men were more prone to suffer from the disease than women (3:1) and urinary infection was a major factor (41.3% in males; 60% in females). Urate stones were found at a higher rate than in western countries, which suggests the possibility of a dietary or even hereditary cause for the condition (Dajani *et al.*, 1981).

Iraq

This country appears to have a very high rate of stone admissions (22/1000 general hospital admissions), with 85% of the patients aged between 18 and 55 years. During the hot season the incidence rises but not to a statistically significant level. Emphasis is placed on climate and industrialisation but no mention is made of bilharzial or schistosomal infection, which is likely to be important in this area (Al-Dabhagh and Fahadi, 1977).

Iran/Turkey

Two important studies of bladder stone disease in children have emanated from each of these countries. The first, from Iran, was clinically orientated and emphasised the urological complications likely to be found in association with vesical calculus (Halim *et al.*, 1981). It showed the effect of urbanisation and improved social status in reducing the incidence. The older study, from Turkey, was again hospital-based but emphasised that on the Anatolian plateau the prevalence of endemic bladder stones was high; the author speculated that diet was likely to be implicated and in particular a substance called bulgar, which is a form of wheat (Eckstein, 1961).

Africa

It is interesting that whereas in the contiguous areas of the Middle East there have been several important studies of stone disease, in-depth studies on the continent of Africa have been largely confined to one country, namely South Africa. In this land of very mixed but distinctive racial groups it has been shown that stone disease in the Bantu races is rare (Modlin, 1969). In a detailed study of this phenomenon the author speculated that the Bantu diet resulted in reduced phosphate excretion together with significantly lower urinary calcium excretion. In a later report the same author considered the effects of unleavened bread, coarse cereals and other similar dietary constituents with a high phytic acid content and suggested that such a dietary pattern can reduce the incidence of stone disease. He used data from countries where the opposite finding was a characteristic of dietary intake, *i.e.* low phytic acid consumption (Modlin *et al.*, 1981).

In the Sudan, vesical calculi are the major problem but the prevalence of upper tract stone disease is increasing. Southern Sudan has a lower incidence than the rest of the country. In subjects living in the north the urine calcium excretion was found to be higher than in those in the south and this was associated with a reduced urinary protein output (Kambal *et al.*, 1981).

Asia

There have been many studies from Asia and in some areas, such as Thailand, the concentration of research projects has revealed some interesting facets of the problem.

India

It has long been recognised that in the northern provinces, including the Punjab, stone disease is common (McCarrison, 1931). A possible explanation could be a reduction in the consumption of vitamin A (McCarrison, 1927). These early Indian studies were probably too non-specific to allow proper epidemiological data to be collected, especially in view of the difficulties of communication at that time. It is of significance in terms of socio-economic development to realise that stone disease of the bladder was still common in certain areas of India and China in 1968 (Singh *et al.*, 1968). In the Manipur area urolithiasis was a common disease, comprising 11.6% of all surgical cases. The authors suggested that Muslims were more likely to develop the condition than tribal people and that Hindus were seven times more likely to develop stones (Singh *et al.*, 1978). This finding could relate to the different dietary habits required by different religions. Hindus are mainly vegetarians, while Muslims eat a more mixed diet which contains meat.

In a specific study of the effects of Tamarest and tartrate as a preventive measure in recurrent stone disease, the authors confirmed the high prevalence of stone disease in Northern India compared with Southern India (Sur *et al.*, 1981).

Thailand

Some of the most interesting work on the differences between people living in different parts of a province within this country was produced by Halstead *et al.* in the early 1960s. Their findings were presented in a series of articles summarised as follows.

(i) There appeared to be a variation in soil chemistry with a peculiar distribution of the incidence of bladder stones (Halstead, 1961). The Chinese appeared to have less of a problem and the small rural populations had a higher incidence than urban dwellers; this contrasts with the findings of other workers. The author speculated on a geographical factor being relevant because of the well defined areas of stone disease.

(ii) Vitamin B was considered to be lacking in the people's diet and in the north of the country bladder stones were more common. Hyperuricosuria was prevalent in children (Gershoff *et al.*, 1963).

(iii) In certain villages, particularly in the north-east, bladder stone disease was common. The authors speculated that among other factors, the consumption of polished rather than unpolished rice and the eating of uncooked fermented fish could explain the different rates of stone formation in the areas studied (Chutikorn *et al.*, 1967; Halstead and Valyasevi, 1967; Halstead *et al.*, 1967; Valyasevi *et al.*, 1967).

Indonesia

In a study of bladder stones in Indonesia it was found that urinary urate was elevated in native children compared with Caucasian children, who have a lower incidence of stone disease. Since rice flour is relatively poor in phosphate content, Brockis *et al.* (1981) suggested that among several possible factors there may be an inadequate buffering mechanism, resulting in the excretion of ammonium acid urate with precipitation of crystals.

Australia

In a study of 619 patients it was found that Australians were most likely to suffer from kidney stone disease between the ages of 20 and 49; 4.7% of calculi were composed of uric acid, which is four times higher than the rate in the United Kingdom, where most of the Australian people originated. Endemic bladder stones were not seen in this study.

In another study from Australia it was found that the indigenous population, *i.e.* the aborigines, did not develop kidney stone disease as did the white population (Bateson, 1977).

Discussion

Most of the above studies were concerned with the relationship between race, diet, climate and other geographical factors. Care should be taken in drawing conclusions from "hospital" statistics. The availability and rate of admission to hospital facilities for the negro population in the southern states of America can seriously bias such figures. Variations in the "incidence" of stone disease can occur simply because of differences in the distribution of population and the concentration or disposal of medical services. There is, however, some evidence that racial factors play an important role in the likelihood of the individual developing stone disease. It can be definitely established from epidemiological studies that improvement in socio-economic factors can eliminate endemic bladder calculi.

There are several interesting observations which merit further study, such as the claim that the Finnish diet has a high magnesium content (Sallinen, 1959); clearly the negro races have a lower incidence of symptomatic stone disease and this may be related to diet (Modlin, 1969).

In recent reviews of the problem in Sweden it was observed that hospital statistics may underestimate the prevalence of stone disease, that the lifetime risk ranges from 10 to 20% for males and 3 to 5% for females and that the disease may be tending to affect younger persons (Ljunghall *et al.*, 1981).

It is common to find in all of these studies based on hospital statistics that men seem to have twice as great a risk of presenting with symptomatic stone disease as women. Some factors, *e.g.* the calcium content of water, which would seem an obvious stone-forming factor, do not appear to be important in determining the incidence of stone disease. Living in rural areas appears to be associated with a reduced incidence of symptomatic disease and those who are more active at work are less likely to be affected than those in sedentary occupations or those who have a high protein content in their diet.

In conclusion, it must be realised that this disease is important, for when it becomes symptomatic it tends to affect patients aged between 25 and 55 years, and they are an important socio-economic group in any population.

A plea must be made for further studies of the natural occurrence of the condition in a variety of different communities, together with an analysis of the lifestyle of these communities. Such studies must be simple and of such a size that they can be repeated at, say, 10-year intervals in order to determine the changing pattern of the disease. A normally non-fatal condition which can be accurately diagnosed by a simple X-ray should be studied early and at given time intervals in order to assess its importance.

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The Author

R. Scott, FRCSE, Consultant Urologist, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.

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Are there Valid Reasons for Using Anti-muscarinic Drugs in the Management of Renal Colic?

R. H. H. TOMIAK, R. B. BARLOW and P. J. B. SMITH

Departments of Urology and Pharmacology, University of Bristol, Bristol

Summary—Experiments have been carried out with isolated ring preparations of human ureter. The tissue displayed spontaneous activity and contracted when exposed to barium chloride (0.5–4 mM) but no responses were obtained with carbachol (0.1 micromolar–0.1 mM). This raises questions about the value of treating ureteric colic with anti-muscarinic drugs.

Though the precise functions of the autonomic innervation of the human ureter are far from clear, it is clinically assumed that the ureter receives a parasympathetic motor supply which is cholinergic and acts on muscarinic receptors in the smooth muscle. Anti-muscarinic drugs are therefore often used clinically as supplementary therapy in the treatment of ureteric colic, where they are believed to reduce the spasm associated with an obstructing calculus. Agents which have been used include atropine, hyoscine butylbromide (Buscopan: Boehringer Ingelheim Ltd.) and propantheline bromide (Pro-Banthine: Searle). However, the pain relief afforded by these drugs is poor and, as with others (Gilman *et al.*, 1980), we are ambivalent as to their efficacy in renal colic. We have therefore carried out *in vitro* experiments with human ureter to check whether it responded to a muscarine-like drug.

Methods

Specimens were obtained from patients (4 male, 2 female) undergoing either nephrectomy or cystectomy for malignant disease. Only one patient had undergone radiotherapy pre-operatively and this did not appear to affect the function of the sample in our tests. Four specimens were from the upper and two from the lower ureter.

Immediately after removal from the patient the samples of ureter were immersed in ice-cold Krebs' solution but with magnesium sulphate replaced by the same concentration of magnesium chloride. A preparation was made by sewing rings together, as described by Macht (1916a): we used five rings. Each was suspended in Krebs' solution and aerated with a mixture of oxygen (95%) and carbon dioxide (5%). The temperature was 37°C. Contractions were recorded isotonically with a load of about 1 g. Drugs were added by a machine controlled from a PET microcomputer (Barlow, 1983) and were allowed to act for 5 min and then washed out. A second wash was given 5 min after this and doses were given once every 15 min.

The viability of the preparations was tested both at the beginning and end of the experiments by adding a drop of 1 M barium chloride: this produced a burst of contractions. In agreement with Macht (1916a), we found that if the tissue was stored at about 4°C it could still be used after 24 h.

Results

With three of the preparations the increase of response with dose was investigated with 1, 2 and 4 millimolar barium chloride and in one experiment 0.5 millimolar was tested as well. The combination of sustained shortening coupled with frequent superimposed contractions is shown in Figure 1a: Figure 1b shows the slightly different type of response obtained in an experiment with lysine vasopressin. The effects were difficult to quantify but it was easy to see that there was usually rather a small response to 0.5 millimolar solutions of barium chloride, a larger response with 1 mM, an even larger response with 2 mM and this was not much less than that produced by 4 mM.

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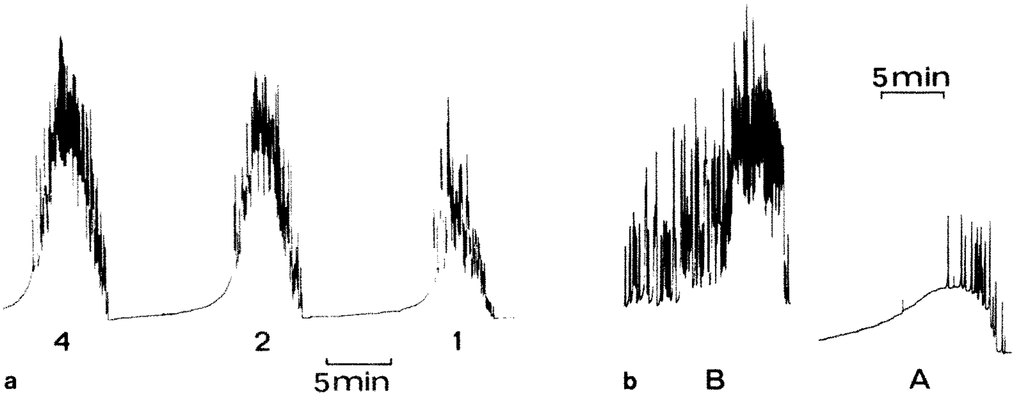

Fig. 1a shows the effects of 1, 2 and 4 mM barium chloride on the preparation obtained by sewing together five rings of human ureter. The record runs from right to left and the tension is measured in arbitrary units. 1b compares the response to lysine vasopressin (0.0186 iu/ml) (A) with that obtained 15 min later with 2 mM barium chloride (B).

Similar experiments were carried out with all of the preparations using carbamylcholine chloride (Carbachol: Sigma) in concentrations of 0.1 micromolar, 1 micromolar, 10 micromolar and 0.1 millimolar. In no instance was there any contractile response. Carbachol was used rather than acetylcholine because it is not hydrolysed by cholinesterase but nevertheless has potent muscarine-like activity. In similar experiments with human bladder (Barlow and Kadow, unpublished data) it produced contractions in concentrations as low as 1 micromolar.

Discussion

Our results question the assumption that muscarinic receptors are associated with the contractile response. Doubts are also raised by the observations of Lapides (1948), who found that subcutaneous injections of 0.25 mg carbachol in man failed to cause a significant increase in ureteric activity, and by *in vitro* experiments with rabbit and rat ureters by Thackston *et al.* (1955). Our results, however, conflict with those of Macht (1916b), who obtained contractions of pig ureter after adding 0.5 ml of an extract obtained by triturating 1 g dried amanita muscaria with 10 ml cold normal saline.

If the motor innervation of the ureter does not involve muscarinic receptors, how should this affect our management of renal colic?

We feel that there seems to be no indication for the administration of pure muscarinic antagonists, such as atropine. From the experiments described above it seems unlikely that they will reduce the spasm caused by an obstructing calculus. There may be some place for administering anti-muscarinic drugs which have additional ganglion-blocking activity, such as Buscopan or propantheline. Although their anti-muscarinic effects are probably irrelevant, their ability to block sympathetic ganglia could be beneficial. It has been demonstrated that blockade of alpha-receptors is useful in the treatment of renal colic (Kubacz and Catchpole, 1972) and blockade of the sympathetic motor innervation at the ganglion might have similar effects. Buscopan and propantheline, however, are only weak ganglion-blocking agents, so there should be scope for improvement in this respect.

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The Authors

R. H. H. Tomiak, MA, MB, BChir, Senior House Officer in Urology.
R. B. Barlow, MA, DSc, Reader in Chemical Pharmacology.
P. J. B. Smith, MChir, FRCS, Consultant Urologist.

Requests for reprints to: R. H. H. Tomiak, Northern General Hospital, Herries Road, Sheffield S5 7AU.

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Use of the Discriminant Index in Dynamic Treatment to Reduce Recurrence of Calcium Oxalate Kidney Stones

S. PERLBERG, R. AZOURY, N. GARTI and S. SARIG

Department of Urology, Hadassah Medical Center and Casali Institute for Applied Chemistry, Hebrew University, Jerusalem, Israel

Summary—Treatment with phosphates, thiazides and allopurinol was undertaken in 54 idiopathic calcium oxalate stone formers, 38 of whom were recurrent stone formers. The patients were followed up for 1½ to 4 years (mean 2.6). During the same period at the pre-treatment stage the patients formed 80 stones, but during therapy only one stone was formed.

A dynamic scheme of therapy was used. Each patient was tested before the start of drug treatment by the discriminant index (DI) method, which measures the overall inhibitory potential to calcium oxalate crystallisation. About 10 days after the start of treatment the DI was tested again. If the response was positive, therapy was continued; if not, the patient was given another drug. Adjustments were made as required.

The stopping of stone formation correlated well with the DI prediction but less well with the hypocalciuric effect of the drugs.

Some of the fundamental studies on the use of drugs in preventing recurrent kidney stone formation were based on an empirical approach (Thomas, 1978), but the investigators soon turned their attention to the rationale for their use. For instance, treatment with thiazides was based on their hypocalciuric action (Yendt and Cohanim, 1978). Later it was thought that the decrease in urinary oxalate during long-term treatment with thiazides might be of equal or even greater importance (Cohanim and Yendt, 1980). A correlation between the rationale and the actual results was not easily proved. On the contrary, a controlled double-blind study showed that a 33% reduction in calcium level did not affect the stone disease (Ettinger, 1976). After it had been shown that allopurinol was effective in the treatment of hyperuricosuric calcium oxalate stone formers (Coe and Raisen, 1973), a partial rationale was provided for the use of this drug in this particular syndrome (Pak *et al.*, 1978a).

Although treatment with drugs has been fairly successful (Coe and Raisen, 1973; Thomas, 1978; Yendt and Cohanim, 1978), there is a need for a deeper understanding of their mechanism of action. Elliot (1983) stated that a group of 117 calcium oxalate stone formers could not be characterised according to any specific abnormality of blood or urine. This conclusion is of general validity and it follows that any changes in urine composition attributable to drug treatment would be unreliable predictors of therapeutic success.

Pak *et al.* (1978b) ascribed the beneficial response to orthophosphate therapy to a decrease in saturation and an increase in the limit of metastability of calcium oxalate. Unfortunately, these effects are not found in all patients. The effect of phosphate treatment, which reduced stone formation in 92% of recurrent stone formers, was also assessed by the modification of the risk factor (P_{SF}) (Heyburn *et al.*, 1982). The percentage of failures was similar to that reported by Thomas (1978) in his long-term follow-up study. It is interesting to note that in a prospective 1-year study of phosphate therapy, 6.2% of patients were judged unresponsive according to the DI test (Sarig *et al.*, 1983).

Although many groups continue to use one-drug

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therapy (Ettinger, 1976) new trends are emerging, such as the "selective therapy" of Pak *et al.* (1981). The seven treatment programmes were chosen because of their ability to correct underlying physicochemical and physiological abnormalities. Another trend is the "comparative approach" used in a multicentre trial to evaluate phosphate thiazide and allopurinol treatment prescribed randomly (Robertson *et al.*, 1984).

In the present study the same three drugs have been used and they were also prescribed randomly. However, the groups of patients were not static, continuing their allotted treatments and determining the relative percentages of failure and success. Instead, soon after starting treatment, our patients were subjected to the DI test described by Sarig *et al.* (1982). This test quantifies the overall inhibitory activity of a tested sample of urine towards the crystallisation of calcium oxalate under specified conditions. The patients who responded favourably to the test were maintained on the initial drug regime. Those who did not respond well were given an alternative drug. Thus a dynamic framework of treatment was devised (Perlberg *et al.*, 1984).

Patients and Methods

Calcium oxalate stone forming patients were subjected to a preliminary screening. Tubular reabsorption of phosphorus (TRP) and nephrogenous cyclic AMP were examined. Patients with suspected hyperparathyroidism were excluded.

The group of 54 idiopathic stone formers included 15 females and 49 males; 38 of them were recurrent stone formers. Their ages ranged from 19 to 67 years (mean 42.3). All had normal kidney function, expressed by creatinine clearance and a normal IVU.

Serum levels of calcium phosphorus, creatinine and uric acid and 24-h urinary excretion of calcium, creatinine and uric acid were measured before starting treatment and then at 3- to 6-monthly intervals.

It was found that 17 patients were hypercalciuric (>300 mg calcium/24 h) and eight were hyperuricosuric (>800 mg uric acid/24 h for females and >850 mg uric acid/24 h for males).

All patients were subjected to the DI test (13) at the pre-treatment stage, and afterwards to repeated tests.

DI test

Details of the DI test (Sarig *et al.*, 1982) and its use in the follow-up of drug therapy (Sarig *et al.*, 1983) have been reported.

Briefly, a solution containing 20% early morning urine is adjusted to 4 mM calcium ion activity. This solution is mixed with a 6 mM equivalent volume of oxalate solution. Precipitation of calcium oxalate starts immediately. The calcium ion concentration decreases gradually and is measured by calcium electrode. The ratio of concentrations after 30 s and 10 min is computed. The logarithm of this ratio is termed DI. DI values range from -0.4 to 2.8. The mean value for stone formers is 1.26 ± 0.24 and for normal subjects 0.41 ± 0.26. The tenth percentile for stone formers is 0.66. In the present study the transformation of DI from a pathological range to a value below 0.66 was the criterion of success.

Drug treatment

The drugs used in this study were Na biphosphate 900-1800 mg daily, chlorothiazide 500-1000 mg daily, and allopurinol 200-400 mg daily.

Scheme of drug treatment

The DI value of each patient was determined at least twice during the pre-treatment stage. The three drugs were almost randomly prescribed, with allopurinol preferred for markedly hyperuricosuric patients. Ten days after the start of treatment the DI was checked. Patients whose DI values fell to less than 0.66 were considered satisfactory and they continued to take the same drug. The dosage was reduced to the lowest level and the DI checked again. If the result was unsatisfactory, the dose was increased and the DI checked, so that the lowest dosage was administered which kept the DI value below 0.66.

If the response at the first trial was unsatisfactory, another drug was administered. The check and appropriate adjustment were repeated (Fig. 1).

When the criterion of success ($DI < 0.66$) was met, the patient was maintained on that treatment with periodical checking of the urinary excretion of calcium, uric acid, creatinine clearance and DI.

The patients in this group were followed up for 18 to 47 months.

Results and Discussion

Details of treatment are shown in Figure 2. Of the 54 patients, 53 had a DI value in the pathological range before the start of treatment. One patient, whose original DI was below 0.66, was kept on a supervised regime of drinking, without drugs. On

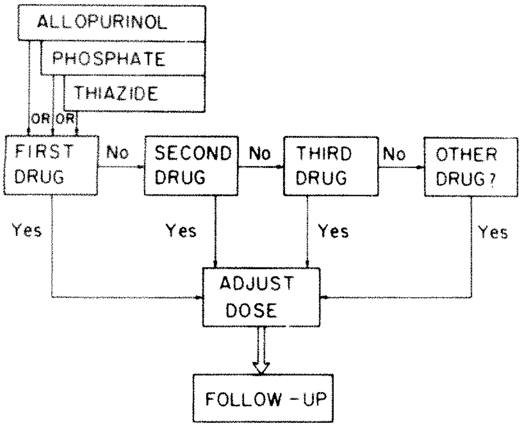

Fig. 1 Dynamic scheme of management of disease using various drugs. Suggestion for criterion of success: DI < 0.66.

the first trial with one of the three drugs, 32 patients responded positively, but two of them had undesirable side effects. Thus the remaining 30 patients—19 on phosphates, 8 on thiazides and 3 on allopurinol—continued the treatment with the drug chosen initially, after adjustment of the dosage. The patients who did not respond well, together with those who showed side effects, were given another drug; 14 responded well, but nine were given the third choice. One of them developed a stone during adjustment of his treatment.

Two patients did not conform to the framework of the management scheme. One, who had abnormally high uric acid excretion (1596 mg/24 h) did not respond well either to allopurinol alone or to allopurinol and phosphates. The final adjustment was allopurinol and thiazides, which reduced the DI to 0.41 and uric acid to 682 mg/24 h. The second interesting case was a hyperuricaemic and hyperuricosuric patient (980 mg/24 h) who developed a stone while on allopurinol treatment. His DI while on the drug regime was 0.95, *i.e.* in the pathological range. He had no previous history of kidney stones which could have justified such high values. When he stopped taking allopurinol for 2 weeks his DI fell to 0.22, *i.e.* within normal limits. He was given no further medication.

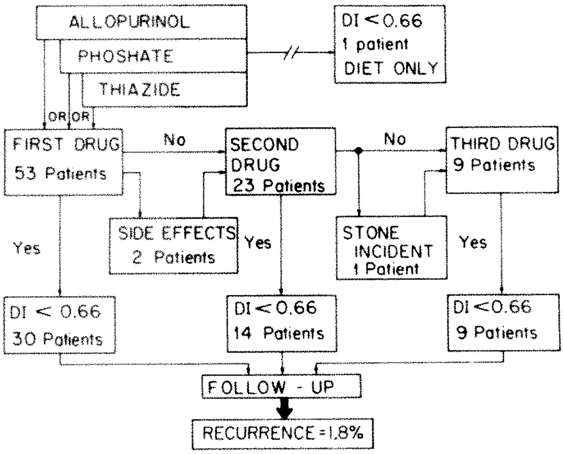

Fig. 2 Flow sheet showing results of compound drug treatment using DI criterion.

The distribution of successful treatments is presented in Table 1. The DI are mean values for the indicated number of patients, computed for their pre-treatment stage, and the values finally obtained with the help of the drugs either on the first or on the ensuing trials.

Table 1 Distribution of Successful Treatments

	Phosphate	*Thiazide*	*Allopurinol*
Number of patients	26	14	12
Mean of DI value before treatment	1.24 ± 0.34	1.14 ± 0.28	1.12 ± 0.39
Mean of DI value after treatment	0.22 ± 0.16	0.28 ± 0.13	0.33 ± 0.14

A small group of four patients did not meet the criterion of DI transformation to the normal range by any of the three drugs used or of their "cocktails". They were excluded from the study and managed with a more detailed metabolic approach.

It must be stressed that the number of patients finally maintained on one of the drugs does not indicate the relative merits of the drugs. The allocation of drugs was not wholly random; since the number of hypercalciuric patients was higher (Melnick *et al.*, 1971) than those with hyperuricosuria (Pak *et al.*, 1978b), it was natural that more phosphate than allopurinol was prescribed at the first trial. Exceptions were made in non-acute cases, to preserve the random character of the first allocation.

It is therefore especially interesting to compare the scheme of management based on DI transformation with the information gained from biochemical data.

The phosphate-responsive group of 26 patients was composed of 12 hypercalciuric and 14 normocalciuric stone formers. In the hypercalciuric group the level of calcium was reduced to normal in nine cases. In two cases it was reduced but did not reach normal level and in one case the calcium excretion was increased. It was also increased to a level above 300 mg/24 h in one of the previously normocalciuric patients. Thus 4 of 26 had a calcium excretion level which was higher than normal. All four patients had been recurrent stone formers for 4 to 25 years. As will be shown later, they stopped forming stones during the period of follow-up.

The thiazide-responsive group included four hypercalciuric patients; two of them reached the normal calcium excretion level and two did not. The remaining 10 normocalciuric patients included one whose calcium levels increased from 280 to 320 mg/24 h). This patient had been a recurrent stone former for 7 years.

In the allopurinol-responsive group there were eight hyperuricosuric patients; in all of them the uric acid level fell to less than 800 mg/24 h, parallel to the DI increase. Some decrease in uric acid excretion was also noted in the normouricosuric patients. Eleven patients in this group were normocalciuric. In one of them, a recurrent stone former for 6 years, the calcium excretion level increased from 244 to 423 mg/24 h. The one hypercalciuric patient showed a decrease in calcium excretion but still remained above normal levels. This patient was a first-time stone former.

There seems to be only one unequivocal chemical response to the drug regime: allopurinol reduces uric acid excretion. The effect of phosphates and thiazides on the change in calcium excretion was much less clear-cut. Of the 17 patients with hypercalciuria only 11 showed a significant decrease in calcium excretion to normal levels. Moreover, three previously normocalciuric patients could be classified as hypercalciuric following what was defined by us as successful treatment. Thus the connection between the DI and the chemical response to drug therapy is weak. The connection has yet to be evaluated between these two criteria and the clinical response, *i.e.* the relationship between the reduction of stone formation rate and the DI response on the one hand and the chemical data on the other.

In Figure 3 the patient-years of the 38 recurrent stone formers and the number of stone incidents are presented. The stone incidents occurred despite all patients being on a high fluid intake. Moreover, the most prolific stone formers received drugs and continued to form stones during the "static" treatment. The last incident occurred just before inclusion in the present study using the dynamic approach. It is difficult to evaluate the number of stone incidents which could have occurred if no preventive treatment had been instituted in this group and in the group of 16 first-time stone formers.

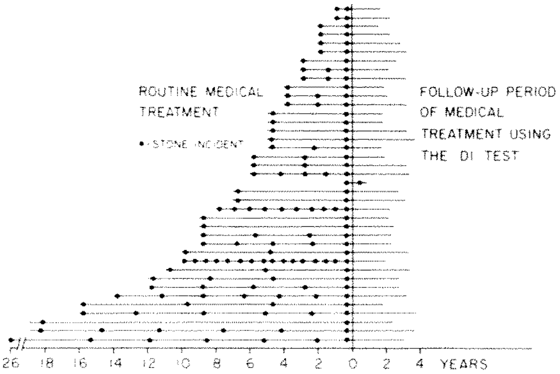

Fig. 3 Effect of dynamic treatment with phosphates, thiazides and allopurinol on new stone formation.

Previous studies have shown that patients with no evidence of metabolic disease, treated by high fluid intake only, had a recurrence rate of 16% during the first 2½ years of follow-up (Gertler, 1971). Sutherland (1954) reported a 16.3% recurrence rate within the first 3 years. The rate of recurrence increases with time; it decreases with medical treatment but still persists. For instance, successful phosphate treatment lowered the rate from 0.66 episodes/year to 0.22 episodes/year for 35 of 38 patients (Heyburn *et al.*, 1982). However, the three unsuccessful patients increased their rate of stone formation over periods lasting up to 4 years.

The present study is of comparable duration. The period of follow-up ranged from 1.5 to 4 years (average 2.6). During 2.6 years about 80 stones were formed at the pre-treatment stage (taking into account the 16 first stones) and only one stone during treatment (Fig. 3).

A comparison between the stone passage rate at the pre-treatment stage and during treatment is detailed in Table 2. The Table follows the scheme adapted by Ettinger (1976) but only studies with comparable periods of follow-up are included. New data have also been added.

Table 2 shows the excellent agreement between DI prediction and stoppage of stone formation in our study. As the correlation between DI prediction and biochemical data was rather weak, it follows that there may be no connection between biochemical data and success of treatment in some cases. Several recurrent stone patients stopped forming stones, though their calcium level did not decline, and in some cases even increased.

Table 2 Effects of Treatment on Stone Passage in Urolithiasis Patients

Reference	*Type of drug*	*No. of patients*	*Mean years of therapy*	*Stone passage*		
				Before therapy	*During therapy*	*% Reduction*
Melnick *et al.* (1971)	Magnesium oxide	142	3	1.43	0.32	77.6
Prien and Gershoff (1974)	MgO-pyridoxine	149	4.1	1.3	0.1	92.3
Pak *et al.* (1978)	Cellulose phosphate	16	2.6	3.8	0.27	92.8
Heyburn *et al.* (1982)	Phosphate	35	up to 4	0.66	0.22	66.7
Ettinger (1976)	Phosphate	25	~4	1.3	0.29	77.6
Present study	Phosphate, thiazide, allopurinol	54	2.6	0.57	0.0077	98.6

A noteworthy phenomenon is that no matter what drug is used, there will remain at least 10% of patients who do not respond (Prien and Gershoff, 1974; Heyburn *et al.*, 1982; Sarig *et al.*, 1983). In the present study the four unresponsive patients were not included in the follow-up. However, the dynamic approach of individual adjustment of drug, according to a set criterion of risk factor, may be advantageous in this respect. The few patients unresponsive to the regular treatment are pin-pointed during the adjustment and efforts may be concentrated on establishing their particular physiological abnormalities.

If the success in reduction of the rate of new stone formation is maintained in further follow-up, the scheme of drug adjustment could be recommended as a regular procedure. The indicative risk factor should be simple, easy to determine and reliable. The DI test fulfils these requirements.

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The Authors

S. Perlberg, MD, Consultant Urologist, Hadassah Hospital.
R. Azoury, PhD, Research student, Casali Institute.
N. Garti, PhD, Professor of Chemistry, Casali Institute.
S. Sarig, PhD, Professor of Chemistry, Casali Institute.

Requests for reprints to: S. Sarig, Casali Institute for Applied Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel.

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Comparison of Urinary Oxalate Excretion in Urolithiasis Patients With and Without Hypercalciuria

T. KOIDE, R. C. BOWYER and J. G. BROCKIS

Department of Surgery, University of Western Australia and Departments of Biochemistry and Urology, Royal Perth Hospital, Perth, Australia

Summary—The relationships between urinary oxalate, calcium and magnesium were investigated in 81 patients with idiopathic calcium oxalate urolithiasis on their regular diets. A significant relationship was established between calcium and oxalate excretion in the analysis of recurrent stone-formers ($n=44$, $P<0.01$), though there was no significant difference between the two in the analysis of the patients overall or in single stone-formers. This suggests that recurrent stone-formers may have some abnormality of oxalate absorption in relation to calcium absorption.

The role of calcium-oxalate interaction in the gut as a cause of mild hyperoxaluria is discussed.

Although the cause of calcium oxalate urolithiasis is multi-factorial, there is no doubt that the urinary supersaturation level of calcium oxalate plays an important role in the first step of calcium oxalate crystal formation.

Recently, among various factors affecting urinary supersaturation of calcium oxalate, mild hyperoxaluria has been recognised with the development of reliable techniques to measure oxalate in biological fluids, such as enzymic analysis, gas chromatography, ion chromatography and isotachophoresis. Several investigators have reported a slight but significant increase in urinary oxalate excretion in patients with recurrent calcium stones (Robertson *et al.*, 1971; Hodgkinson, 1974) and also in patients with both single and recurrent calcium stones (Yachiku *et al.*, 1980; Wallace *et al.*, 1981; Hesse *et al.*, 1984). Robertson and Peacock (1980) have emphasised that hyperoxaluria, even of a mild degree, is an important risk factor in calcium oxalate stone formation.

With regard to the pathogenesis of such mild hyperoxaluria, some researchers (Hodgkinson, 1974, 1978; Dobbins *et al.*, 1981; Bataille *et al.*, 1983; Erickson *et al.*, 1984) have put forward an interesting hypothesis that the concentration of free calcium in the gut influences the absorption of oxalate and, therefore, there should be a close relationship between the absorption of calcium and oxalate in the gut.

The cause of mild hyperoxaluria, however, remains questionable in patients on a normal diet because most of the oxalate found in urine is a final endogenous product and oxalate ingested which is poorly absorbed accounts for a relatively small percentage of the whole (Hodgkinson, 1977; Williams and Smith, 1983).

The aim of this study was to clarify the role of calcium in the absorption of oxalate in calcium oxalate stone-formers on a regular diet.

Patients and Methods

Patients

The series comprised 81 patients with stones consisting predominantly of calcium oxalate who attended the Outpatient Clinic at the Royal Perth Hospital from June to December 1984. There were 65 males and 16 females aged 43.9 ± 13.7 years (mean ± 1SD). Forty-four patients were recurrent stone-formers and 37 patients had only a single stone episode.

A detailed interview regarding dietary habits, including supplementary ascorbic acid intake, was carried out in order to exclude patients with abnormally balanced meals Patients with impaired renal function, enteric disorders and proven cause of stones were also excluded.

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Table 1 Comparison of Urine Volume, Oxalate and Magnesium Excretion between all Patients with and without Hypercalciuria (Mean ± 1 SD)

	No.	*Urine vol. (ml)*	*Oxalate (μmol/day)*	*Mg (mmol/day)*
Patients without hypercalciuria	55	1385 ± 457	354 ± 104	3.6 ± 1.4
		***	N.S.	***
Patients with hypercalciuria	26	1575 ± 501	382 ± 160	5.3 ± 2.0

N.S.: not significant (Student's t test)
***: $P < 0.001$ (Student's t test)

Table 2 Comparison of Urine Volume, Oxalate and Magnesium Excretion between Recurrent Stone-formers with and without Hypercalciuria (Mean ± 1 SD)

	No.	*Urine vol. (ml)*	*Oxalate (μmol/day)*	*Mg (mmol/day)*
Patients without hypercalciuria	28	1439 ± 487	346 ± 105	3.8 ± 1.4
		**	**	***
Patients with hypercalciuria	16	1732 ± 532	417 ± 165	5.1 ± 1.7

**: $P < 0.01$ (Student's t test)
***: $P < 0.001$ (Student's t test)

Biochemical examinations

Biochemical analyses of plasma and 24-h urines were performed. We measured various components of plasma (Na, K, Ca, Pi, Mg, urate, creatinine and C-iPTH) and 24-h urine (volume, Na, K, Ca, Pi, Mg, oxalate, urate and creatinine).

Two different 24-h urine specimens were collected, one being acidified in advance with 25 ml 6M HCl for the measurement of components other than urate.

Oxalate measurement

Urinary oxalate concentration was measured by a discrete batch analyser using the enzymic method reported by Potezny *et al.* (1983) and following the precipitation procedure of Mazzachi *et al.* (1984).

Results

Incidence of hypercalciuria

According to the normal upper limit of calcium excretion on a normal diet used in the Royal Perth Hospital (7.5 mmol/day), 26 of 81 patients (32%) were hypercalciuric. These 26 patients with hypercalciuria were males aged 42.2 ± 11.0 years (mean ± 1 SD); the patients without hypercalciuria comprised 39 males and 16 females aged 44.7 ± 14.8 years (mean ± 1 SD).

We also divided the patients into recurrent stone-formers and single stone-formers, and then divided them in the same manner as the above. We obtained 16 recurrent stone-formers with hypercalciuria, 28 recurrent stone-formers without hypercalciuria, 10 single stone-formers with hypercalciuria and 27 single stone-formers without hypercalciuria. The age of each group was 43.4 ± 10.2, 46.4 ± 13.0, 42.9 ± 16.2 and 40.2 ± 11.9 years (mean ± 1 SD) respectively.

Differences in urine volume between patients with and without hypercalciuria

The volume of urine in patients with hypercalciuria was significantly larger than in those without hypercalciuria in the analysis of all 81 patients as well as recurrent stone-formers ($P < 0.01$) (Tables 1 and 2) but there was no significant difference between them in the analysis of single stone-formers (Table 3).

Relation between urine volume and urinary oxalate excretion

A weak but significant positive correlation was noted between the daily amount of urinary oxalate excretion and the daily volume of urine (correlation coefficient (r) = 0.2303, $P < 0.05$).

Table 3 Comparison of Urine Volume, Oxalate and Magnesium Excretion between Single Stone-formers with and without Hypercalciuria (Mean ± 1 SD)

	No.	*Urine vol. (ml)*	*Oxalate (μmol/day)*	*Mg (mmol/day)*
Patients without hypercalciuria	27	1330 ± 417	364 ± 101	3.4 ± 1.3
		N.S.	N.S.	***
Patients with hypercalciuria	10	1325 ± 314	325 ± 133	5.6 ± 2.3

N.S.: not significant (Student's t test)
***: $P < 0.001$ (Student's t test)

Relation between urinary oxalate and calcium excretion

In the analysis of all 81 patients there was no significant correlation between urinary oxalate and calcium and there was no significant difference in oxalate excretion between patients with and those without hypercalciuria, despite a weak trend that the more patients excreted calcium, the more they excreted oxalate into the urine (Table 1).

When the analysis was limited to recurrent stone-formers, however, those with hypercalciuria excreted significantly larger amounts of oxalate than those without hypercalciuria ($P < 0.01$) (Table 2). A significant correlation was also noted between oxalate and calcium excretion in the analysis of recurrent stone-formers (correlation coefficient (r) = 0.2765, $P < 0.01$).

In the analysis of single stone-formers there was no significant correlation between calcium and oxalate excretion. There was also no significant difference in oxalate excretion between patients with and those without hypercalciuria (Table 3).

Relation between urinary oxalate and magnesium excretion

In the analysis of all of the patients as well as in the analysis of single stone-formers, there was no significant correlation between urinary oxalate and magnesium; in the analysis of recurrent stone-formers only, however, a significant correlation was found between the two (correlation coefficient (r) = 0.6714, $P < 0.001$).

Relation between urinary calcium and magnesium excretion

A significant positive correlation was observed between the amount of calcium and magnesium excreted into the urine in the analysis of all 81 patients (correlation coefficient (r) = 0.5022, $P < 0.001$), in the analysis of the recurrent stone-formers (correlation coefficient (r) = 0.3875, $P < 0.001$), and also in the analysis of the single stone-formers (correlation coefficient (r) = 0.5936, $P < 0.01$).

Discussion

Conventional techniques for oxalate measurement have, until recently, either lacked reliability or been very complicated and only a few reports have been acceptable. The enzymic method, coupled with an acidic precipitation procedure, is one of the recent improvements in the techniques of measuring urinary oxalate, since it minimises the influence of ascorbic acid on the results (Mazzachi *et al.*, 1984).

Hyperoxaluria, even of a mild degree, has been recognised as an important risk factor in calcium oxalate stone formation (Robertson and Peacock, 1980), so that the absorption of oxalate from the gut has become a matter of concern. It has been proved that a large oxalate intake leads to marked hyperoxaluria (Butz *et al.*, 1980; Finch *et al.*, 1981; Vahlensieck *et al.*, 1984). It has also been shown that restriction of dietary calcium promotes urinary oxalate excretion (Marshall *et al.*, 1972; Bataille *et al.*, 1983) and that abundant intraluminal calcium in the gut reduces the absorption of oxalate (Hodgkinson, 1978; Dobbins *et al.*, 1981). It has also been reported that the amount of oxalate excreted in the urine tends to increase in stone-formers with hypercalciuria (Hodgkinson, 1974; Marangella *et al.*, 1982; Bataille *et al.*, 1983). We feel, however, that the cause of hyperoxaluria in patients with idiopathic calcium oxalate urolithiasis cannot be fully explained by the interaction of calcium and oxalate in the gut. Epidemiological studies and a recent investigation by Schwille *et al.* (1984) have raised the question of whether this interaction is the main cause of mild hyperoxaluria.

Many investigators have found similar values for urinary oxalate excretion in countries where people have different dietary habits (Hodgkinson and Williams, 1972; Thomas *et al.*, 1973; Hallson and

Rose, 1974; Tiselius, 1977; Yachiku *et al.*, 1980). In particular, the average daily intake of calcium in Japan has been about 13.75 mmol/day (550 mg/day) for the last 10 years or more (Ministry of Health and Welfare of Japan, 1983), while that of other Western countries ranges from 23.25 to 30 mmol/day (930 to 1200 mg/day) (Robertson *et al.*, 1979; Bagnall, 1982; Itokawa, 1983; Vahlensieck *et al.*, 1984). Why does this large difference in calcium intake not affect the amount of urinary oxalate excretion, even though it is accepted that calcium bio-availability is affected by various foodstuffs other than oxalate (Allen, 1982)? Although no firm data are available, the daily amount of oxalate intake in Japan seems to be similar to that in Western countries. The same oxalate-rich foods, such as spinach, peanuts, chocolate, tea, *etc.*, are eaten, though not rhubarb and beetroot. Moreover, the amount of calcium corresponding to the average daily intake of oxalate has been estimated to be about 1.44 mmol/day (130 mg/day) (Hodgkinson, 1977). This is quite a small amount, so it is doubtful whether a lack of intraluminal free calcium really occurs even in patients with absorptive hypercalciuria on their normal diet. In other words, Western patients with absorptive hypercalciuria should have more free calcium in their gut on their normal diet than Japanese patients. Since some epidemiological studies have shown no obvious difference in the pattern of stone disease between Japan and Western countries (Asper, 1984), it might be inappropriate to emphasise the role of oral calcium as the cause of mild hyperoxaluria without considering other foodstuffs affecting calcium bio-availability, or to look on a disturbance of oxalate absorption as the single cause of mild hyperoxaluria without taking endogenous metabolism into account.

A recent study by Schwille *et al.* (1984) suggested that the source of the post-prandial excess of urinary oxalate in patients with idiopathic hypercalciuria is uncertain but that exogenous oxalate as a source can be ruled out because the excess oxalate excretion is seen after an oxalate-free meal.

In this study a significant relationship was noted between urinary oxalate and calcium in the analysis of recurrent stone-formers, whilst there was no significant relationship between the two in the overall analysis of the patients or in the analysis of single stone-formers. This suggests that recurrent stone-formers may have some abnormality of oxalate absorption related to calcium absorption. It is possible that recurrent stone-formers may have some fault in their gut which promotes not only oxalate absorption but also calcium absorption. If there were no such abnormality in the gut and intestinal calcium-oxalate relationships played the most important role in regulating oxalate absorption, we should have obtained similar results in the analysis of the single stone-formers, unless the abnormality which we postulate had disappeared by the time our analyses were carried out. We agree that intraluminal calcium-oxalate interaction must be one of the factors affecting the amount of urinary oxalate, but that some mechanism other than intraluminal calcium-oxalate interaction causes the mild hyperoxaluria.

We also found a significant correlation between urinary oxalate and magnesium in the analysis of recurrent stone-formers, but it is not possible at this stage to establish any causative relationship. Certainly the solubility of magnesium oxalate is much greater than that of calcium oxalate (Hodgkinson, 1977). The main source of magnesium in Western countries is milk and milk products (Itokawa, 1983), which can in itself explain the strongly significant correlation between urinary calcium and magnesium in the statistical analysis of all of our patients as well as in that of recurrent stone-formers. The role, therefore, of oral magnesium should probably not be emphasised in the absorption of oxalate in the gut.

There has been some discussion as to whether the amount of oxalate excretion is related to the volume of urine (Yachiku *et al.*, 1980; Finch *et al.*, 1981; Hesse *et al.*, 1984). We found a significant correlation between urine volume and oxalate excretion ($P < 0.001$), the urine volume of patients with hypercalciuria being larger than that of patients with normocalciuria. Once again, it is not possible to invoke a causative relationship from this finding.

In conclusion, despite the hypothesis that it is the lack of intraluminal calcium in the gut which promotes the absorption of oxalate, and that this could explain the mild hyperoxaluria shown in recurrent stone-formers, it remains doubtful whether the calcium-oxalate relationship in the gut is really the main cause. In order to clarify the exact role of oral calcium in the genesis of mild hyperoxaluria, pan-nutritional studies, including fatty acid and fibre intake, will be required on a large number of patients and further invesitagion into the endogenous metabolism of oxalate will be needed.

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The Authors

T. Koide, MD, Research Fellow, University of Western Australia, and Clinical Assistant in Urology, Osaka University, Japan.

R. C. Bowyer, BSc, FAACB, PhD, Biochemist, Royal Perth Hospital.

J. G. Brockis, ChM, FRACS, Associate Professor, University of Western Australia, and Urologist, Royal Perth Hospital.

Requests for reprints to: T. Koide, Department of Urology, Osaka University Hospital, Fukushima 1-1-50, Fukushima-Ku, Osaka 553, Japan.

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Rapid Ward Assessment of Renal Function by Reflectance Photometric Determination of Plasma Creatinine

I. GIBB, P. CROSS, D. PRATT and R. R. HALL

Departments of Clinical Biochemistry and Urology, Freeman Hospital, Newcastle upon Tyne

Summary—The Ames Seralyzer reflectance photometer and disposable reagent strips for the determination of plasma creatinine were evaluated in the laboratory and on a urology ward over a 3-month period. Principles of the instrument used are described, as are details of the evaluation procedures. Reproducibility of results under optimum conditions gave coefficients of variation $<7\%$. Under routine conditions of use, medical staff and laboratory analysts achieved high correlation with the routine laboratory method of analysis ($r=0.986$, $N=108$: $r=0.996$, $N=102$ respectively). Potential sources of inaccuracy were identified. Seralyzer determination of plasma creatinine can be rapidly, simply and reliably performed by medical staff on a urology ward, thereby facilitating assessment of renal function governed by clinical requirement rather than by laboratory convenience.

Qualitative and semi-quantitative visually interpreted urine dipstick tests are widely used in ward siderooms and out-patient clinics. Recent technological advances in such dry strip chemistry and in the field of reflectance photometry have resulted in a growing potential for the performance of rapid, simple, but quantitative plasma/serum biochemical analyses on the ward and in other decentralised locations (Weiner, 1980; Marks, 1983). The greatest impact of these techniques to date has been in blood glucose monitoring, but the simple reflectance meters used are generally limited to this single analysis.

A benchtop reflectance photometer with multianalyte capability, the Ames Seralyzer (Ames Division, Miles Laboratories, UK) has recently become available along with a range of dry strip serum chemistries (Zipp, 1981), allowing determination of a variety of metabolites, enzymes and drugs. Test strips are available with which serum/plasma creatinine concentrations may be determined in 30 s. Since plasma creatinine can be used to estimate glomerular filtration rate (GFR) (Cockcroft and Gault, 1976), or its reciprocal value plotted, as this parallels changes in GFR, the system offers the potential for rapid assessment of renal function. We therefore undertook an evaluation of the Seralyzer and disposable creatinine test strips to assess their suitability for renal function monitoring by medical staff in the urology ward or outpatient clinic.

Methods

1. Seralyzer operation for plasma creatinine determinations

The Seralyzer (Fig. 1) is a microprocessor-controlled benchtop reflectance photometer measuring 38 × 26 × 12 cm. The disposable creatinine test strips consist of a reagent area bonded to a bar-coded plastic support strip. The strips are supplied in bottles of 50 and are stable for 1 year unopened and for 60 days after opening if kept at room temperature. In use, the strip is placed on a sliding table, 30 μl of plasma are pipetted on to the test area, the start button is pressed and the table

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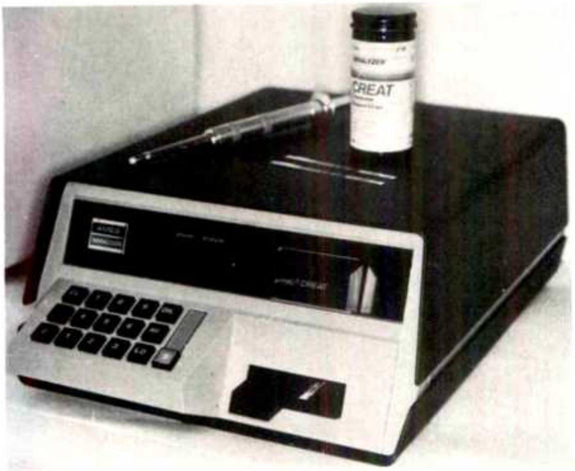

Fig. 1 Seralyzer reflectance photometer with bar-coded disposable creatinine test strips and automatic pipette.

pushed into the measuring position. The rate of change of reflectance from the test surface is automatically monitored as a purple colour develops on the strip at a rate proportional to the concentration of creatinine in the test sample. After 30 s this concentration is digitally displayed, accompanied by an audible alarm. A flashing display indicates a concentration exceeding the instrument range (up to 1326 µmol/l) and that dilution and re-analysis of the sample may be required.

The instrument is calibrated by analysis of high and low calibrators supplied by the manufacturer, and this is currently recommended on a weekly basis or when changing the batch of test strips or calibrators. The instrument self-monitors malfunctions and some operator errors, indicating such events audibly and by flashing coded error messages on the display panel.

2. *Laboratory assessment*

Test precision was assessed by replicate analysis of fresh human plasma pools, using a single instrument calibration and batch of test strips. The pools were then frozen in small volumes and analysed on 20 consecutive days using different calibrations, different batches of test strips and different operators. Daily analysis of these pools was also performed with the routine laboratory plasma creatinine method based on the widely used Jaffe reaction on a Technicon SMA 6/60 continuous flow analyser (Technicon, USA). Accuracy of Seralyzer analyses over the same 20 days was assessed by comparison with results obtained on routinely submitted plasma samples. Quality control materials were also reconstituted daily and analysed by both methods.

3. *Ward-based assessment*

Venous blood from patients on a urology ward was collected into lithium heparin tubes. Plasma was separated for Seralyzer analysis in the ward side-room and then sent to the laboratory for routine creatinine determination. Only samples required for normal patient care and investigation were collected over a 6-week period. A fresh control sample, for which the acceptable range of creatinine concentration had been determined on the Seralyzer and which was known to the medical staff, was provided each day. This was analysed twice with every batch of samples, the analyses being performed only if the control determinations fell within the acceptable range. Up to four unknown samples were also provided daily, in order to monitor instrument performance independently.

Results

The results of the within-batch laboratory study on pooled plasmas are presented in Table 1 and these indicate the optimum reproducibility of the test at three different plasma creatinine concentrations. Table 2 presents the comparative laboratory per-

Table 1 Within-batch Precision of Seralyzer Creatinine Results using Pooled Plasmas at Three Creatinine Concentrations. (N = 10 in all cases)

	Pool 1	*Pool 2*	*Pool 3*
Mean (µmol/l)	86	151	406
Standard deviation	4.2	6.6	28.0
CV (%)	4.9	4.4	6.9

Table 2 Between-batch Precision Data from Three Plasma Pools Measured on the Seralyzer (A) and by the Routine Laboratory Method (B). (N = 20 in all cases)

		Pool 1	*Pool 2*	*Pool 3*
	Mean (µmol/l)	78	153	379
(A)	Standard deviation	5.6	11.2	22.7
	CV (%)	7.2	7.3	6.0
	Mean (µmol/l)	75	150	378
(B)	Standard deviation	6.2	2.2	5.1
	CV (%)	8.3	1.5	1.3

formances of the Seralyzer and the routine laboratory method, again at three different creatinine concentrations over 20 days. During this time the Seralyzer was calibrated seven times, three batches of test strips were used and two operators performed the analyses. These data represent the reproducibility of the test under more variable conditions. Student's *t* testing showed no significant differences between the mean creatinine concentrations for the Seralyzer and the routine method ($P < 0.05$), but Fisher variance analysis showed the Seralyzer precision to be significantly poorer at the same level for two of the three pools.

During the first few days of the ward evaluation 16 plasmas were analysed in duplicate on the Seralyzer. The mean creatinine concentration was 325 µmol/l (range 86-895) and the coefficient of variation for the paired data was 4.4%. Subsequent samples were analysed singly on this basis.

In Table 3 the relative performances of laboratory analysts and doctors using the Seralyzer for quality control material analyses are compared with the routine laboratory method. These materials are used by laboratories to assess day-to-day method reproducibility and accuracy. Although there were no differences in mean values or levels of precision between doctors and laboratory staff using the Seralyzer ($P < 0.05$), data from both groups of users showed statistically significant differences in these values from the routine laboratory method.

Table 3 Batch-to-batch Performances of Seralyzer for Laboratory Analysts (A) and Doctors (B), Compared with the Routine Laboratory Method (C)

	Quality control materials		
	Level 1	*Level 2**	*Level 3*
(A) Mean (µmol/l)	99	276	847
Standard deviation	9.7	21.9	60.7
CV (%)	9.8	7.9	7.1
N	30	30	30
(B) Mean (µmol/l)	106	276	850
Standard deviation	11.9	24.7	70.3
CV (%)	11.2	8.9	8.3
N	18	46	20
(C) Mean (µmol/l)	77	197	761
Standard deviation	4.7	3.6	7.2
CV (%)	6.1	1.8	0.9
N	20	20	20

* Used as control during ward evaluation

During the laboratory evaluation 102 patients' plasmas were analysed comparatively, yielding the relationship Y (Seralyzer) = 1.02 X (SMA) + 0.057. The correlation was 0.996, the mean Seralyzer plasma creatinine 284 µmol/l (range 47-1077) and the mean SMA plasma creatinine 291 µmol/l (range 45-1103). Results of a similar comparison of methods when doctors performed the Seralyzer determinations on 108 patient's samples over 6 weeks are presented in Figure 2. The mean Seralyzer plasma creatinine concentration for this series was 214 µmol/l (range 66-810) and the mean SMA result was 209 µmol/l (range 55-862). Figure 3 shows the comparative trends in 10 patients whose plasma creatinines were measured on the Seralyzer and with the routine method on more than one occasion during the ward evaluation.

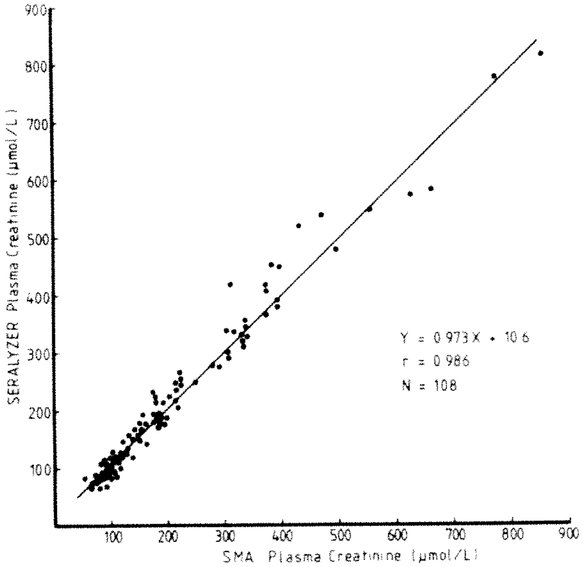

Fig. 2 Comparison of plasma creatinine results obtained by medical staff using the Seralyzer system with the routine laboratory method.

In both stages of the evaluation a small number of samples gave Seralyzer results which did not correlate well with the routine method. Frankly icteric plasmas gave higher apparent concentrations on the Seralyzer and those with visible haemolysis gave apparently lower concentrations. The manufacturer does warn of these limitations in the package insert accompanying the creatinine test strips.

Discussion

Analytical systems being considered for decentra-

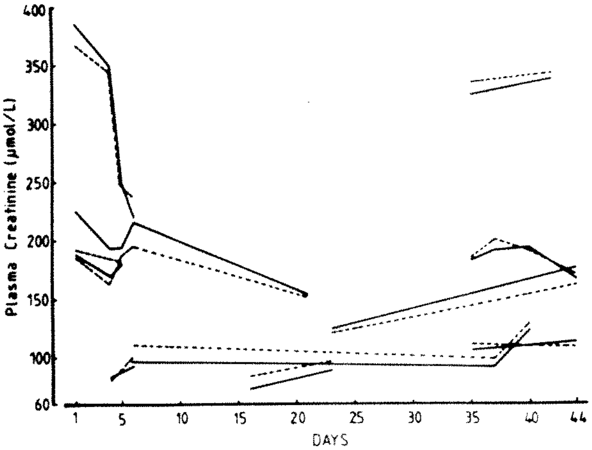

Fig. 3 Comparative serial monitoring of plasma creatinine in 10 patients. (Solid lines: Seralyzer; broken lines: routine laboratory method).

lised use must be simple to operate, accurate, precise, economical, reliable and offer appropriate analyses. Determination of plasma creatinine with the Seralyzer proved to be a simple procedure and medical staff with little experience of analytical manipulations were able to produce meaningful data after only 20 minutes' instruction. The major potential pitfalls are poor pipetting technique and failure to start the measuring cycle immediately after the plasma has been applied to the strip.

Accuracy of Seralyzer plasma creatinine determinations was extremely good, both groups of users achieving a high degree of correlation with the routine laboratory method. The main sources of inaccuracy appeared to be the presence of elevated concentrations of bilirubin or haemoglobin in test plasmas. This may account for the significant differences between the mean quality control results for the two methods, as these materials contained abnormal concentrations of bilirubin (51-108 μmol/l) which did not significantly interfere with the routine method.

Precision or reproducibility of an analytical test is of fundamental importance in assessing the suitability of that test for use. The desirable level of precision may be judged on a variety of bases (Fraser, 1980), but the current consensus is that biological variation of the analyte of interest is the most appropriate yardstick (Proceedings of the Subcommittee on Analytical Goals in Clinical Chemistry, 1979). For plasma creatinine in individual testing and serial testing on an individual, in order to aid diagnosis or monitor therapy, the analytical coefficient of variation should not exceed 2.2% (Elevitch, 1977). This target was not achieved at any level with the Seralyzer and, significantly, only achieved at elevated plasma concentrations with a routine laboratory method which is commonly used throughout this country. Clearly, present creatinine chemistries are not capable of attaining the highest goals for excellence of analytical precision. The similar performances of medical and laboratory staff using the plasma creatinine strip method are consistent with a recent laboratory evaluation of the system (Stevens *et al.*, 1983). Furthermore, in serial monitoring of plasma creatinine, the analytical precision routinely achieved by medical staff gave similar information on the individual trends in real function to that provided by the laboratory data.

The Seralyzer is relatively inexpensive, costing £2900, and disposable creatinine strips cost 21.6p each (both excluding VAT). This compares with a laboratory cost for a creatinine determination of 17p as part of an SMA urea and electrolyte profile. Throughout the 3-month evaluation the Seralyzer proved extremely reliable, suffering no breakdowns of any description. Should such occur, Ames undertake to supply a replacement instrument, generally within 24 h. Laboratory support during ward use was limited to periodic instrument calibration and daily provision of quality control materials.

We believe it is appropriate that urologists and nephrologists should have the facility to assess renal functional status in their patients rapidly and simply, free from the constraints of normal laboratory hours and work patterns. While individual creatinine determinations can be rapidly performed, we consider it most appropriate that the system be used for discretionary testing in acute situations and in out-patient clinics. In this respect the value of the system assessed has been greatly enhanced by the development of a disposable strip chemistry for the measurement of plasma potassium.

The introduction of ward-based analytical equipment raises an additional number of practical issues, particularly those of the cost of supplying and maintaining the equipment, training and retraining ward staff in the use of the equipment and the need to ensure adequate and sustained levels of technical performance by those staff. Given the high cost of emergency pathology laboratory call-outs, appropriate location of the Seralyzer could result in savings in the laboratory budget. Additionally, judicious use of the instrument in out-patient departments and in acute care situations can facilitate earlier diagnosis and improved patient management (Gibb *et al.*, 1985), thereby yielding savings in the clinical budget. These combined economies should more than offset the capital and revenue consequences of using some decentralised analytical equipment. The rudimentary skills necessary to operate the analyser are easily acquired and the training of new ward personnel would not impose a major burden on the laboratory support service. Furthermore, the use of a quality control monitoring system such as described in this report would largely ensure the ongoing technical competence of ward-based users and thus maximise the value of the instrument in urological practice.

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The Authors

I. Gibb, MSc, CChem, MRSC, MCB, Principal Biochemist, Department of Clinical Biochemistry.

P. Cross, MB, ChB, Senior House Officer, Department of Urology.

D. Pratt, BSc, Biochemist, Department of Clinical Biochemistry.

R. R. Hall, MS, FRCS, Senior Lecturer and Consultant, Department of Urology.

Requests for reprints to: I. Gibb, Department of Clinical Biochemistry, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

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Comparison of Dynamic Computed Tomography, Diuresis Renography and DTPA Parenchymal Transit Time in the Assessment of Dilatation of the Upper Urinary Tract

D. E. NEAL, W. SIMPSON, P. BARTHOLOMEW and P. M. KEAVEY

Departments of Radiology, Medical Physics and Urology, Newcastle General Hospital and Freeman Hospital; Department of Surgery, University of Newcastle, Newcastle upon Tyne

Summary—Three methods of assessment of upper urinary tract dilatation were compared prospectively. Forty-eight dilated renal units (35 patients) were studied, the majority being idiopathic pelvic hydronephrosis (69%).

Dynamic computed tomography (CT) involves rapid sequence CT after injection of contrast medium. The maximum enhancement of a medullary region of interest (MMR) and its rate of enhancement (SMS) were derived from dynamic CT. Dynamic CT was compared with diuresis probe renography and measurement of parenchymal transit time (PTT) from DTPA imaging.

The MMR (70.1 ± 10.6 HU) and SMS (2.0 ± 0.5 HU/s) in controls were significantly greater than in patients with upper tract dilatation (52.8 ± 18.5 and 1.43 ± 0.85 HU/s; both $P < 0.001$). A significant association was observed between impairment of renal function in patients with upper tract dilatation and a low SMS and MMR ($P < 0.01$).

Statistically significant agreement was observed between the results of diuresis renography and PTT ($P < 0.025$). However, no significant agreement was found when the results of dynamic CT were compared with either diuresis renography or with PTT.

Dynamic CT as performed in the present study has no useful contribution to make in the diagnosis of patients with dilatation of the upper urinary tract.

The finding of upper tract dilatation in a patient with loin pain is the prelude to the question of whether operation should be performed in order to alleviate symptoms and to protect the kidney from future damage. However, identification of obstruction and prediction of risk to the kidney are difficult.

Obstruction may produce dilatation of the collecting system and impairment of kidney function. The magnitude of renal impairment is dependent upon several factors, including the degree of completeness of the obstruction, its mode of onset—whether it is acute or chronic—and the presence or absence of urinary infection (Wilson, 1980; Wright and Howards, 1981).

Obstruction leads to an elevation of intrapelvic pressure at high rates of urinary flow and to poor ureteric run-off. This concept is the basis of the Whitaker test (Whitaker, 1979) and of the diuresis renogram (O'Reilly *et al.*, 1978). Acute obstruction leads to a temporary elevation of intrapelvic pressure (Michaelson, 1974) and, if present for more than 24 h, results in a decrease in renal blood flow and glomerular filtration rate (Moody *et al.*, 1975). These abnormalities, in combination with the increase in tubular absorption of sodium that has been noted in acute obstruction (Abbrecht and Malvin, 1960), may result in slow parenchymal

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transit: hence the hypothesis that measurement of parenchymal transit time by deconvolution analysis may be useful in the diagnosis of obstruction of the upper urinary tract (Britton *et al.*, 1979).

Each of these three methods—the Whitaker test, diuresis renography and measurement of PTT—has disadvantages. First, and most important, there is no "gold standard" in the diagnosis of obstruction. Pressure flow studies are invasive and employ infusion rates well in excess of physiological rates of urine production. Also, falsely low pressures may occur (Bratt *et al.*, 1982). Diuresis renography suffers from the disadvantages that some kidneys with poor function may fail to respond to the diuretic and that results in grossly dilated kidneys may be equivocal. Measurement of parenchymal transit time by deconvolution analysis correlates well with pressure flow studies (Britton *et al.*, 1979). However, regions of interest that exclude the collecting system from the parenchyma may be difficult to define.

Computed tomography permits good morphological resolution of the renal parenchyma. In addition, a sequence of scans may be taken to follow contrast medium through the cortex and medulla—dynamic CT (Brennan *et al.*, 1979). By defining a region of interest over part of the cortex and part of the medulla it is possible to record the CT number sequentially, thereby obtaining data relating to the renal handling of the contrast medium. We thought that such data should permit measurement of the transit of contrast medium through the kidney and so give an objective measurement of the presence of obstructive nephropathy. We therefore carried out a study to compare dynamic CT, diuresis renography and PTT in the evaluation of patients with upper tract dilatation.

Patients and Methods

Thirty-five patients (25 male, 10 female; mean age 40 ± 16 years) were studied. Each had upper urinary tract dilatation on IVU (48 abnormal units; Table 1). Idiopathic pelvic hydronephrosis was diagnosed in 33 of the 48 units (69%) and recurrent obstruction after pyeloplasty was suspected in 9 of the 33.

Table 1 Clinical Diagnosis in 48 Dilated Renal Units

Idiopathic pelvic hydronephrosis	33
Stones	2
Retroperitoneal fibrosis	3
Megaureters	3
Horseshoe kidneys and ? PUJ	2
Ureteric strictures	5

Twenty-two control patients (28 units) were studied by means of dynamic CT. Six patients (12 units) who were undergoing CT in the management of malignant disease had apparently normal kidneys. The remaining 16 patients had unilateral dilatation; the contralateral, apparently normal kidney was taken as a control.

The three studies were performed within 2 weeks of each other. The patients were asked to attend for the studies in a well hydrated condition. Each of the three studies was evaluated without prior knowledge of the results of the other tests.

Diuresis renography

Probe renography with computer assisted blood background correction was performed using a method similar to that described by Britton and Brown (1968). Intravenous urography was used to localise the kidney. Each detector incorporated a "D"-shaped collimator with a thick medial septum which enabled a wide field of view to be counted but which minimised cross-talk from the opposite kidney. A bolus injection of 0.8 MBq of ^{131}I-labelled Hippuran was given intravenously. An injection of frusemide (Lasix) (dose being determined by serum creatinine) was given after 10 to 15 min. After completion of the Hippuran study, *in vivo* blood labelling was performed using ^{113m}In; this allowed a correction to be made for non-renal contributions to the field of view. The percentage relative function was calculated from the relative heights of the background corrected renogram traces between 2 to 3 min after injection. If delayed drainage was present, the response to frusemide was defined as follows:

(i) No response on a rising curve: obstructed.
(ii) Significantly improved drainage: atonic.
(iii) Equivocal response (included with the atonic group).

Measurement of parenchymal transit time by deconvolution analysis

The basis of the test has been described previously (Britton *et al.*, 1979): 100 MBq of ^{99m}Tc labelled DTPA were injected and a dynamic study of 100 frames (64 × 64) of 10s each was acquired on the gamma camera. Time activity curves were obtained for parenchymal and pelvic regions of interest (ROI). Deconvolution analysis was carried out using counts from a ROI over the left ventricle as the input function. Parenchymal transit time (PTT:

measured in seconds) was calculated after subtracting the shortest transit time (Britton *et al.*, 1979). The upper limit of normal for PTT in control kidneys was 150 s.

Dynamic CT

This was carried out using a Picker Synerview 1200 SX operated in its automatic mode. A bolus of 40 ml of Urografin 310 M (meglumine diatrizoate) was injected (5 ml/s). Each scan lasted 3 s and was performed every 13 s. Only 8 to 12 scans could be performed, giving a total available time for study after injection of between 91 and 143 s. The scan was carried out at a level which included the central part of each kidney. Part of the medulla over a pyramid and part of the cortex were selected as separate regions of interest. Several medullary regions were sampled. Retrospectively, that yielding the shortest and steepest rise in CT number was chosen as the medullary ROI. Each ROI consisted of a cylinder 10 mm long and 1 to 2 mm in diameter.

Typical curves over the cortex and medulla are shown in the Figure. Three parameters were derived from these curves: the maximum cortical rise (MCR) was the maximum rise in CT number measured over the cortical ROI immediately after the initial steep rise. The maximum medullary rise (MMR) was the maximum CT number reached in the first 90 s after injection of contrast. The steepest medullary slope (SMS) was the steepest rate of increase in the CT number measured over the medullary ROI.

Definition of impaired renal function

Impairment of function of a renal unit was defined if the percentage relative function was less than 40% on renography or if the serum creatinine was greater than 140 µmol/l.

Statistical methods

The results are quoted as means (± 1 SD). Differences between results were assessed by means of Student's *t* test for non-paired data. Differences in frequency were assessed by means of the chi-squared test with correction for continuity.

Results

Controls

The mean values for the parameters derived from dynamic CT of the two groups of controls were similar (patients with malignancy: MCR 70.5 ± 17 HU; MMR 66.3 ± 10.5 HU; SMS 2.0 ± 0.5 HU/s: radiologically normal kidney of patients with dilatation: MCR 73.4 ± 21 HU: MMR 72.4 ± 10.3 HU; SMS 2.0 ± 0.5 HU/s. These data were combined to give the following results: MCR 71.6 ± 19.4 HU; MMR 70.1 ± 10.6 HU, SMS 2.0 ± 0.5 HU/s. Lower limits were then defined (mean—2 SD: MCR 32.8 HU; MMR 48.9 HU; SMS 1.0 HU/s). Renal units with values below the lower limits for the MMR or the SMS or both were classified as abnormal.

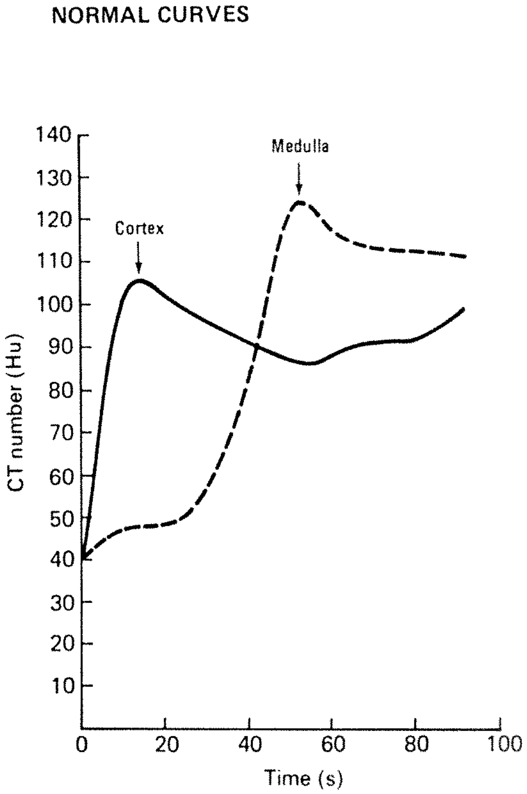

Fig. Diagram showing enhancement of the CT number over cortical and medullary regions of interest after injection of contrast in a control. The arrow over the cortical curve shows the maximum cortical rise and that over the medullary curve shows the maximum medullary rise. The maximum rate of increase in CT number before the maximum medullary rise was reached is the steepest medullary slope.

Patients with upper tract dilatation

Forty-eight renal units were studied by means of diuresis renography and dynamic CT but only 39 were studied by means of PTT. Five renal units were difficult to classify by means of diuresis renography (10.5%). These were considered most appropriate for inclusion in the atonic, non-obstructed group.

Dynamic CT in patients with upper tract dilatation

The MMR (71.6 ± 19.4 HU) and SMS (2.0 ± 0.5 HU/s) in controls were significantly greater than the MMR (52.8 ± 18.5) and SMS (1.43 ± 0.85; both $P<0.001$) in patients with upper tract dilatation.

Presence of impaired renal function

Significant agreement was found between impaired renal function and an abnormal SMS ($\chi^2=9.14$; $P<0.01$) or an abnormal MMR ($\chi^2=9.14$; $P<0.01$) but an abnormal MCR was not associated with impairment of renal function ($\chi^2=0.78$; $P-$NS). Significant association was also found between impaired renal function and obstruction diagnosed either by diuresis renography ($\chi^2=5.27$; $P<0.025$) and by measurement of PTT ($\chi^2=5.98$; $P<0.025$).

Abnormal results

The overall frequency of abnormality observed in the three groups was similar (diuresis renography—46%; dynamic CT—44%; PTT—51%). However, important differences between the three tests were found when individual renal units were compared (Table 2).

Table 2 Comparison of Classification of Renal Units by Means of Dynamic CT, Diuresis Renography and PTT

		CT: Normal	*Abnormal*
Diuresis renography	Atonic	17	9
	Obstructed	10	12
		PTT: Normal	*Abnormal*
CT	Atonic	13	8
	Obstructed	6	12
		PTT: Normal	*Abnormal*
Diuresis renography	Atonic	15	7
	Obstructed	4	13

When diuresis renography and PTT were compared, statistically significant agreement was found. In 28 of the 39 renal units the results were in agreement ($\chi^2=5.97$; $P<0.025$). On the other hand, no significant agreement was found between the presence of abnormalities diagnosed on dynamic CT and obstruction diagnosed by either diuresis renography ($\chi^2=1.2$; $P-$NS) or by PTT ($\chi^2=2.1$; $P-$NS).

Discussion

The most important finding of this study was that the results of dynamic CT did not correlate well with the results of either diuresis renography or measurement of PTT.

The original hypothesis was that if obstruction results in a decrease in renal transit time, the rate of appearance in the medulla of injected contrast medium when measured by means of dynamic CT would be a good estimate of renal transit time and would, therefore, predict the presence of obstruction. There are a number of reasons why our data do not support this hypothesis.

Firstly, there are several potential difficulties in interpretation of the CT scan. For technical reasons, we were limited to carrying out approximately 10 scans (one every 13 s). Therefore, only a small number of data points could be collected during the initial, steeply rising part of the medullary curve. Whilst it was usually easy to distinguish cortex and medulla unless there was considerable atrophy of the cortex, overlap of the medullary ROI with renal cortex or pelvicaliceal system may have occurred on occasion.

Secondly, the steepest medullary slope (SMS) is probably not related solely to transit of contrast medium through the kidney. For example, medullary blood flow and the concentrating ability of the nephron will also affect the SMS. Both of these factors may be impaired by chronic obstruction (Suki *et al.*, 1966; Wilson, 1972; Wilson, 1980; Wright and Howards, 1981) and this may be the explanation for the good agreement that we found between abnormal results of dynamic CT and impaired renal function.

Other authors using similar methods to perform dynamic CT have quantified their results differently (Heinz *et al.*, 1980; Ishikawa *et al.*, 1981; Treugut *et al.*, 1981; Probst *et al.*, 1983; Reisser *et al.*, 1984). However, we did not find that information of additional value was provided by their methods.

The agreement that was found between diuresis renography and measurement of PTT deserves comment since the concepts underlying their application to the diagnosis of upper tract obstruction appear to be different (O'Reilly *et al.*, 1978; Britton *et al.*, 1979). One reason for this concordance may be that both tests correctly, but by different means, identify the majority of patients with obstruction. However, other explanations may be applicable. Overlap of the parenchymal ROI and the pelvicaliceal ROI may occur during measurement of PTT in patients with a very dilated pelvis. Also, high count rate activity originating in the renal pelvis may contribute to activity seen in the cortex. This cross-talk between the two regions of interest could produce a false increase in PTT. Both of these situations may lead to spurious agreement between the results of PTT and diuresis renography.

The limitations of tests used to assess upper tract dilatation lead to equivocal results and therefore to difficulties in clinical management. At present, the use of dynamic CT in these difficult cases does not appear to help the urologist to decide whether obstruction is present or not.

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The Authors

D. E. Neal, MS, BSc, FRCS, First Assistant, Department of Urology, Freeman Hospital, and University Department of Surgery.

W. Simpson, FRCR, MB, Consultant Radiologist, Newcastle General and Freeman Hospitals.

P. Bartholomew, BSc, Physicist, Newcastle General Hospital.

P. M. Keavey, MSc, Senior Physicist, Freeman Hospital.

Requests for reprints to: D. E. Neal, Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

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The Role of the Ileal Conduit in the Development of Upper Tract Dilatation

D. E. NEAL, T. HAWKINS, ANN S. GALLAUGHER, D. M. ESSENHIGH and R. R. HALL

Departments of Urology and Medical Physics and University Department of Surgery, Freeman Hospital, Newcastle upon Tyne

Summary—The purpose of this study was to clarify the role of the conduit in the development of upper tract dilatation after ileal conduit urinary diversion. Twenty-seven patients with a normal upper tract were compared with 17 who had developed upper tract dilatation. Patients were studied by means of a technique to measure pressure and flow under "steady-state" conditions.

Pressure activity was classified into two types. Type I pressure activity (frequency 6.2 ± 3/min; amplitude 4.7 ± 3 cm H_2O) resulted in to-and-fro movement of contrast and the escape into the appliance of small volumes of contrast. In controls, most of the output from the conduit occurred during type I activity (73 ± 14%). Type III/IV pressure activity resulted in vigorous aboral peristalsis and occurred infrequently in controls (frequency 5 ± 4/h). In patients with upper tract dilatation, in contrast, type III/IV peristaltic activity occurred frequently (frequency 37 ± 30/h; $P < 0.001$; amplitude 72 ± 34 cm H_2O) and was responsible for most of the output (70 ± 17%; $P < 0.001$).

The findings support the hypothesis that high pressure activity in the conduit is an important factor in the aetiology of upper tract dilatation, and they are compatible with the presence in such patients of functionally important obstructions of the distal conduit.

In recent years it has become clear that the long-term results of ileal conduit diversion are poor (Dunn *et al.*, 1979; Pitts and Muecke, 1979; Neal, 1985). For example, Dunn and his colleagues reported that in a group of 67 children followed up for 10 years no fewer than 82% suffered from late complications. Of particular concern was the finding that progressive, bilateral upper tract dilatation developed in 28%. The cause of such dilatation is often obscure (Scott, 1973; Rickwood, 1982).

It has long been suspected that in the presence of free ureteric reflux, high pressure in the conduit may be an important factor in the development of upper tract dilatation. In acknowledgement of this theory, various surgical techniques have been used in the hope of diminishing reflux (Leadbetter and Clarke, 1955; Bergman and Nilson, 1974). However, even when anti-reflux procedures are performed in colonic conduits the long-term results are poor, the rate of reflux and ureteric stricture formation being high (Elder *et al.*, 1979).

The mode of emptying of the ileal conduit has been studied previously by methods such as radiological screening (Campbell *et al.*, 1965; Kafetsioulis and Swinney, 1970), measurement of basal pressure (Dybner *et al.*, 1972; McEwan and Clark, 1973) and measurement of pressure activity during infusion of fluid (Weiss *et al.*, 1975; Magnus, 1977). However, some of the methods used in these studies to assess the function of the conduit may have led to difficulties in interpretation. For instance, obstruction may result if intraluminal balloons are used to record pressure, and rapid infusion of fluid or feeding (Sarr and Kelly, 1980) may induce small bowel activity. Furthermore, if flow along a small bowel segment is to be measured, then motility within that segment should be monitored simultaneously (Sarr and Kelly, 1980; Kerlin *et al.*, 1982). These conditions have not been met by previous studies.

The aim of the present study was to test the hypothesis that high pressure activity within the conduit is an important factor in the development of upper tract dilatation. We also wished to study the rate of transit along and the rate of efflux from the conduit.

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Patients and Methods

Forty-four patients with an ileal conduit were studied. Each had a normal upper tract before operation. One group (controls, n = 27) had retained normal upper tracts after diversion; the other group (study patients, n = 17) had developed progressive bilateral upper tract dilatation of obscure aetiology within the preceding 6 years. Each patient had been investigated by IVU and in each patient a loopogram had demonstrated free ureteric reflux, although eight controls (30%) and six study patients (35%) had undergone the formation of an anti-reflux anastomosis (Leadbetter and Clarke, 1955).

The mean age of controls (mean 50 ± 17 (SD) years) was similar to that of study patients (57 ± 20 years). The proportion of women in the control group (52%) was not significantly different from that in the study group (35%). Twenty-one patients (11 controls; 10 study patients) had been treated for bladder cancer and 15 (8 controls and 7 study patients) had received radiotherapy. The remaining 23 patients had undergone urinary diversion in the treatment of neurological disease affecting the bladder or incontinence. The period of follow-up after diversion was at least 5 years (controls 11 ± 6 years; study group 13 ± 5 years).

The patients attended for the study having fasted for 12 h, but were well hydrated. Prophylactic antibiotics were given to patients with recurrent urinary infection. A triple lumen tube (12F) was passed to the proximal end of the conduit under radiological screening: it proved impossible to insert in three additional patients who were excluded from the study. A note was made of the site of any difficulty encountered during insertion of the catheter. Effluent was collected into a modified urostomy appliance. Patients were studied on an X-ray table and screening was performed at intervals.

Pressure recording

Pressure was recorded from two channels—2 cm and 10 cm from the tip of the catheter; the remaining channel was used to infuse fluid into the conduit via the tip of the catheter. The pubic symphysis was taken as zero reference point and respiration was monitored by means of a pneumograph. The pressure recording channels were perfused with saline (at room temperature) at high pressure (400 cm H_2O) but at low flow (0.1 ml/min). Occlusion of the catheter resulted in a pressure rise of 50 cm H_2O/s (Kerlin *et al.*, 1982).

Protocol

Contrast medium at room temperature (15% sodium diatrizoate; 480 mOsm/l) was infused at a rate of 10 ml/min for 15 min. The infusion rate was then decreased to 5 ml/min for 15 min and then to 2 ml/min for a basal period of 15 min. This protocol was adopted in order to establish standard basal conditions for each patient. The study proper then began.

Measurement of transit

An injection of 0.1 mCi (3.7 MBq) of ^{99m}Tc colloid in 0.2 ml was made into the tip of the catheter. Pressure was monitored continuously for a further period of 30 min, video monitoring being carried out during different types of pressure activity. Effluent was collected at 1-min intervals. These samples were weighed and the amount of radioactive marker measured by means of a gamma radiation analyser. The counts were corrected for decay and compared with a "standard" equivalent to the dose of original marker.

The recovery of marker was assessed by calculating the cumulative percentage recovery 20 min after injection and also by calculating the time taken for the amount of recovered marker (counts/min/g) to decay from peak to half peak recovery (Fig. 1).

Analysis of pressure recordings

The terminology described by Code *et al.* (1957) and Hightower (1968) was adopted in analysing the pressure waves (Fig. 2). Type I pressure activity is of low amplitude (usually less than 10 cm H_2O), low frequency (about 8/min) and does not alter baseline pressure. Type III/IV waves are associated with peristalsis, are of high amplitude, elevate basal pressure and may have a complex waveform.

To measure the frequency and amplitude of type I pressure activity, the recording was divided into minute sections (excluding periods of type III/IV activity) and the median value was determined. The frequency of type III/IV pressure activity was determined by counting each episode (frequency/h). Absent pressure activity was defined if only respiratory activity was present for more than 1 min. All reported results were derived from the pressure recording channel situated 2 cm from the tip: the proximal channel was used to determine the presence of propagation.

Statistical analysis

The data are presented as means ± 1SD. Statistical significance was assessed by means of the Mann

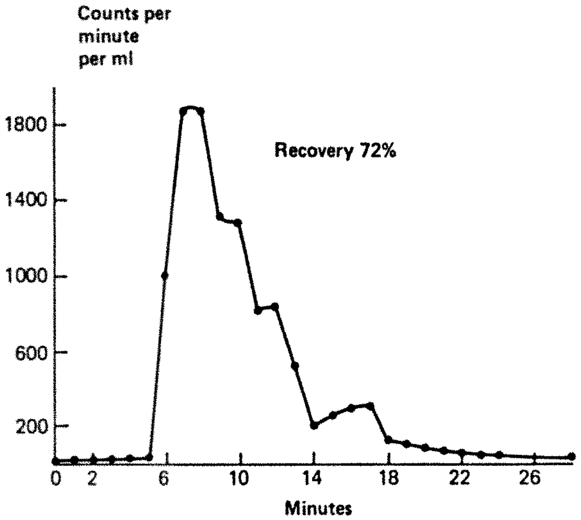

Fig. 1 Diagram demonstrating recovery of the radioactive marker in one of the controls.

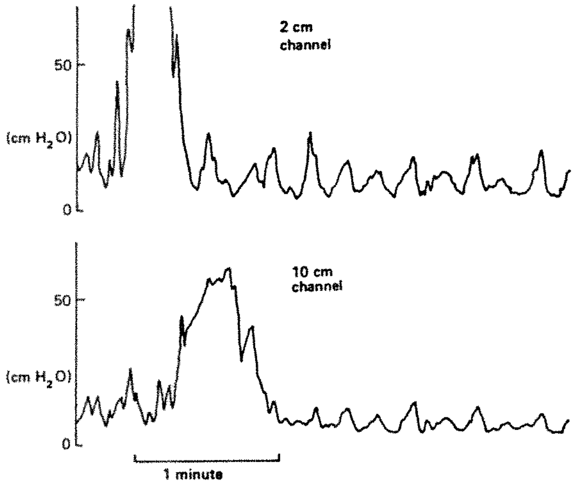

Fig. 2 Pressure recording of one of the controls. A peristaltic pressure wave (type III/IV activity) is shown progressing in an aboral direction along the conduit. Type I activity is also shown.

Whitney U test and the chi square test with correction for continuity (Siegal, 1956). The study had the approval of the Newcastle Ethical Committee.

Results

Insertion of the catheter

Difficulty and temporary hold-up during insertion of the catheter were encountered in the region of the stoma, abdominal wall or distal conduit in 6 controls (22%) and in 12 study patients (71%; $\chi^2 = 8.2$; $P<0.01$).

Pressure and video recording

Basal pressure in study patients was significantly greater (11.7 ± 5 cm H_2O) than it was in controls (4.8 ± 3 cm H_2O; $P<0.001$).

The frequency and amplitude of type I pressure activity in study patients (f = 7.0 ± 2/min; a = 6.0 ± 5 cm H_2O) was similar to that seen in controls (f = 6.2 ± 3/min; a = 4.7 ± 3 cm H_2O). During type I activity to-and-fro movement of contrast occurred with the escape into the appliance of small volumes of contrast.

Type III/IV activity occurred infrequently in controls (4.8 ± 3/h). Peristalsis was invariably identified during this type of activity and the efflux from the stoma increased in volume, most of the contrast in the distal conduit being ejected from the stoma.

The frequency of type III/IV pressure activity in study patients (36.7 ± 30/h) was significantly greater than that observed in controls ($P<0.001$). The amplitude of such pressure activity in study patients (72.2 ± 34 cm H_2O) was also greater than in controls but this did not achieve statistical significance (47.1 ± 34 cm H_2O; $0.05<P<0.1$).

Retrograde peristalsis was not identified in controls but was observed in two patients with upper tract dilatation. At later laparotomy, both patients were found to have had the conduit fashioned in a reversed direction.

Periods of apparent inactivity lasting for more than 1 min were observed in controls (mean duration = 10 ± 12% of the study period) and in study patients (mean duration = 6 ± 11%). In three controls and one study patient, type I pressure activity was absent for more than 30% of the study period.

Relationship of pressure and flow

The output from the conduit in controls (5.3 ± 2 ml/min) was similar to that observed in study patients (5.2 ± 2 ml/min). However, marked differences in the pattern of emptying were observed on further analysis.

In both groups, the output during type I pressure activity (study group: 2.3 ± 2 ml/min; controls: 3.9 ± 3 ml/min) was less than that observed during type III/IV pressure activity (study group: 9.2 ± 8 ml/min; controls: 12.5 ± 7 ml/min; both $P<0.001$). For both types of pressure activity, however, the output of patients with upper tract dilatation was less than that of controls ($P<0.05$).

As observed previously, the frequency of type III/IV activity was greater in study patients than in controls. In consequence, the proportion of the cumulative output from the conduit that occurred during type III/IV pressure activity in patients with upper tract dilatation (70 ± 17%) was significantly greater than in controls (27 ± 16%; $P<0.001$). Hence in patients with upper tract dilatation, most of the output from the conduit occurred during high pressure type III/IV activity (72.2 ± 34 cm H_2O), whereas in controls, most of the output from the conduit occurred during low amplitude, type I pressure activity (4.7 ± 3 cm H_2O).

Recovery of infused marker

The amount of radioactive marker recovered 20 min after injection was significantly greater in control patients (77.3 ± 13%) than in study patients (48.6 ± 22%; $P<0.001$). The rate of fall in recovery after peak value (from peak to peak/2) was also greater in controls (3.12 ± 2 min) than in study patients (7.1 ± 6 min; $P<0.05$).

Discussion

The most important finding was that the function of the ileal conduit was clearly abnormal in patients with upper tract dilatation. These abnormalities included high basal pressures, the frequent occurrence of high pressure type III/IV peristaltic activity and expulsion of effluent mainly by type III/IV pressure activity. These findings are consistent with the presence of functionally important obstruction of the distal conduit in some patients. In controls, the mode of emptying of the conduit appeared to be by means of low pressure, to-and-fro movement of its content, presumably supplemented by ureteric peristalsis.

The slow recovery of marker that was observed in patients with upper tract dilatation could be explained by a combination of free ureteric reflux and high pressure activity in the conduit, the dilated upper tract acting as a reservoir.

The catheter that was used to measure pressure in the conduit is unlikely to have caused the abnormalities that we observed, firstly because of its small diameter, and, secondly, because the abnormalities were not identified in controls. Likewise, the rate of infusion that we used (2 ml/min) is within the physiological range of urine flow. The terminology that we adopted to describe the pressure activity (Foulk *et al.*, 1954; Code *et al.*, 1957; Hightower, 1968) is not now in common use: currently, the migrating nature of the pressure and myoelectric activity of the small bowel is emphasised (Szurszewski, 1969; Code and Marlett, 1975). For several reasons we have not analysed our recordings in such a manner. Firstly, it would have been necessary to measure the motility of the conduit synchronously with that in the region of the small bowel from which the conduit had been constructed: identification of this segment of intact bowel would have been difficult. Secondly, the utility of this approach is open to doubt since the motility of the isolated small bowel segment (the conduit) is not necessarily related temporally to that of the remaining small bowel. Whilst some authors have found that construction of an isolated small bowel loop fails to abolish the temporal association between the migrating myoelectric complex of the small bowel and that seen on the isolated segment, others have observed that this relationship is disturbed. Thirdly, the motility of an isolated segment may be altered by perfusion. For example, Sarr and Kelly (1981) found that perfusion of an isolated small bowel loop lengthened the period of the migrating complex, both on the loop and on the remaining small bowel. For these reasons we have concentrated on measuring pressure activity in the conduit whilst simultaneously monitoring efflux.

It seems unlikely that our findings could be explained by neuromuscular inco-ordination of the conduit due to damage to its innervation, since even complete division of the nerve supply to an isolated segment of small bowel was found not to abolish the appearance of the migrating myoelectric complex on the loop (Sarr and Kelly, 1980).

Our findings are most readily explained by the presence of functional obstruction in the region of the distal conduit. Most authors have observed that type III/IV pressure activity occurs infrequently in normal small bowel (Horowitz and Farrar, 1962) except during phase 3 of the migrating myoelectric complex—which lasts for only a few minutes. Although Code *et al.* (1957) observed that type III/IV activity occurred frequently in two patients with ileostomies, their method—using large water-filled balloons—may have induced obstruction. It is well documented that small bowel obstruction results in the appearance of vigorous peristaltic activity (Sperling, 1938). Clinically inapparent but functionally important obstruction in the region of the distal conduit due to narrowing or kinking is the most likely explanation for our findings.

Certain observations on the physiology of the ileal conduit are in keeping with our findings. For example, "voiding pressures" in the conduit were noted to be raised in patients with obstruction (Weiss *et al.*, 1975) and in patients with a normal upper tract, the most common type of contraction observed in the conduit was of the to-and-fro type (Campbell *et al.*, 1965; Kafetsioulis and Swinney, 1970; Weiss *et al.*, 1975). Authors who have reported a high frequency of peristaltic contraction (Magnus, 1977) used a balloon catheter inflated in the distal conduit and instilled fluid at irregular rates, techniques which might have caused obstruction and induced peristaltic activity.

Empirically, it has been found that good results may follow a thorough stomal revision in patients with upper tract dilatation when it is carried out in those in whom "good" peristalsis is observed—even in the absence of obvious stomal narrowing (Rickwood, 1982). Our hypothesis, that functional obstruction of the conduit is an important factor in the development of upper tract dilatation, is in keeping with this observation. The hypothesis developed from this study needs to be tested further by determining the clinical and physiological effects of surgical attempts to relieve the proposed obstruction.

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We thank Mr W. K. Yeates for permission to study his patients and for his constructive criticism of the project. We thank the technical staff of the Department of Medical Physics who prepared the radiochemicals. D. E. Neal is supported by the Northern Counties Kidney Research Fund and the William Leech Property Trust.

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The Authors

D. E. Neal, MS, FRCS, First Assistant, Department of Urology and University Department of Surgery.

T. Hawkins, BSc, Principal Physicist, Department of Medical Physics.

Ann S. Gallaugher, Technician, Department of Medical Physics.

D. M. Essenhigh, ChM, FRCS, Consultant Urologist.

R. R. Hall, MS, FRCS, Consultant Urologist.

Requests for reprints to: D. E. Neal, Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

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Morphological and Morphometric Studies of the Human Obstructed, Trabeculated Urinary Bladder

S. A. GILPIN, J. A. GOSLING and R. J. BARNARD

Department of Anatomy, University of Manchester and Department of Urology, Withington Hospital, Manchester

Summary—As part of an ongoing study on trabeculation of the human urinary bladder, morphological and morphometric techniques have been employed on biopsy samples of detrusor muscle removed from control and urodynamically obstructed patients. In control material the mean profile area, profile diameter and nucleated profile percentage of bladder smooth muscle cells were determined. The values of the same parameters were obtained for smooth muscle cells in samples from urodynamically obstructed and endoscopically trabeculated patients. Comparison of the results obtained from the two groups showed that smooth muscle cells undergo compensatory hypertrophy in response to outflow obstruction. Furthermore, connective tissue infiltration of detrusor muscle bundles is a characteristic of those bladders which possess cells showing the largest increase in cell size.

In a preliminary study describing the histological features of the non-neurogenic trabeculated urinary bladder, Gosling and Dixon (1980) reported that connective tissue infiltration of smooth muscle bundles takes place in the absence of muscle cell hypertrophy. These findings were based on a subjective evaluation of histological sections prepared from bladder biopsy samples of trabeculated and control specimens. Since objective criteria were not employed in this earlier investigation, the possibility exists that significant changes in muscle cell size may have been overlooked. Consequently the present investigation has sought to provide morphological data on the dimensions of detrusor muscle cells using specific quantitative techniques. The results obtained using these methods have been correlated with detailed pre-operative urodynamic and endoscopic evaluation of the patients studied. By so doing it was hoped to provide additional information on the changes in detrusor smooth muscle cell morphology which accompany bladder trabeculation.

Patients and Methods

The histological material was obtained from patients in whom detailed clinical examination had failed to demonstrate the presence of neurological disease. All patients were assessed urodynamically prior to cystoscopic evaluation. Urodynamic evidence of outflow obstruction was deemed to be present when a detrusor pressure rise greater than 100 cm of water and a flow rate of less than 10 ml/s were recorded.

At endoscopy the bladder wall was assessed subjectively by the same observer and trabeculation was recorded using an arbitrary four-point scale (absent, mild, moderate, severe). During endoscopy biopsy samples were removed from selected sites and rapidly frozen in 2-methyl-butane cooled in liquid nitrogen. Cryostat sections 10μ in thickness were prepared under standard conditions and stained using Masson's trichrome technique. For the purposes of the present study detailed histological and morphometric analyses of biopsy samples were carried out on the material obtained from two groups of patients. The first group served as controls and consisted of patients in whom urodyna-

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mic assessment was normal and trabeculation was judged to be absent. Thirty-seven patients (age range 20–72 years, mean 46 years) were included in this group and comprised 25 patients with symptoms suggestive of interstitial cystitis but whose bladders, at cystoscopy, appeared normal, six patients with bacterial cystitis, five with urothelial tumours and two with stress incontinence. The second group consisted of those patients in whom unequivocal urodynamic evidence of outflow obstruction was accompanied by severe bladder trabeculation as assessed endoscopically. This group comprised 14 patients (age range 66–76 years, mean 71 years), of whom 12 were male.

Histological Assessment

Each sectioned biopsy sample was initially assessed to determine the presence or absence of connective tissue infiltration of smooth muscle bundles. During this evaluation non-infiltrated bundles were identified which were sectioned either in transverse or longitudinal planes and subsequently used for morphometric analyses (see below). Those bundles judged to be sectioned transversely were used to determine smooth muscle cell mean profile area, diameter and nucleated profile percentage. Longitudinally sectioned bundles were employed to assess nuclear length.

Cell Mean Profile Area

Mean profile areas (MPA) of smooth muscle cells were assessed according to a point counting technique. Using a 25 × 25 cm grid lattice divided into 625 1-cm squares, a measure of the total area per print occupied by smooth muscle was obtained by counting the number of grid square intersections which fell at random on smooth muscle cell profiles. The MPA of smooth muscle cells was then calculated by dividing the value obtained for total muscle area by the total number of smooth muscle cell profiles on each photograph. At least 500 muscle cells per patient were counted.

Cell Profile Diameter and Nucleated Profile Percentage

Using the photomicrographic prints prepared from six control and six obstructed, severely trabeculated patients, a calibrated circle lattice was employed to determine cell profile diameter. The lattice consisted of 30 circles with diameters of 1 to 30 mm in increments of 1 mm. The circle lattice was placed over the profile of individual muscle cells and the size of circle which was the closest fit recorded for each cell. For each patient, muscle cell profiles with the same diameter were expressed as percentages of the total number of muscle cells.

Using the prints of smooth muscle cells sectioned transversely, the percentage of smooth muscle cell profiles containing nuclei was calculated for 12 control and 12 obstructed patients.

Measurement of Nuclear Length

In this part of the study, tissue sections cut parallel to the long axis of smooth muscle cell bundles were identified in samples from 12 patients in each group. Photomicrographic prints of longitudinally sectioned smooth muscle cells were prepared and the mean nuclear length determined by direct measurement.

Appropriate statistical analyses of data included Fillibens normal distribution method, correlation and regression methods, Student's *t* test and the Mann-Whitney U-test.

Results

Detrusor Morphology

1. *Control*

Histological examination of biopsy samples from patients in this group showed the detrusor to consist of compact, interweaving bundles of smooth muscle. Connective tissue infiltration of muscle bundles was absent in all of the material examined (Fig. 1).

2. *Obstructed trabeculated*

Of the 14 patients studied, 12 provided biopsy samples showing evidence of connective tissue infiltration of some, but not all, smooth muscle bundles (Fig. 2). Material from the remaining two patients was devoid of connective tissue infiltration and was histologically indistinguishable from control preparations.

Morphometric Data

1. *Mean profile area (MPA)*

Using correlation and regression analyses in control specimens, the smooth muscle cell mean profile area was not significantly affected by the age of the patient (Fig. 3). Furthermore, significant sex differences in the value of MPA for males (47.00 ± 4.49 μ^2) and females (47.1 ± 1.33 μ^2) were not demonstrated.

Using the biopsy material from patients all of whom had outflow obstruction, severe trabeculation and connective tissue infiltration, the MPA of

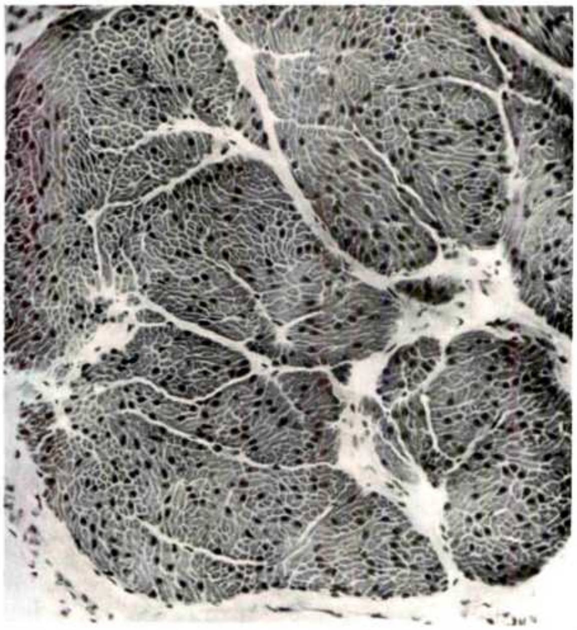

Fig. 1 Detrusor bundles from a control patient showing compact transversely orientated smooth muscle bundles. (Masson's trichrome technique × 126).

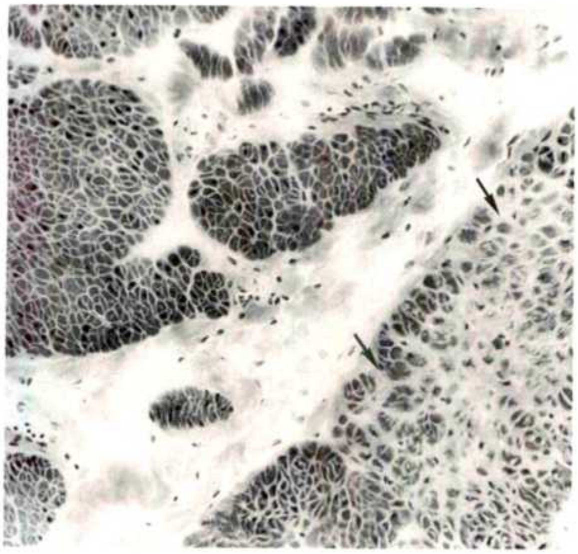

Fig. 2 Detrusor muscle from an obstructed trabeculated bladder showing compact (apparently normal) bundles lying adjacent to a muscle bundle (arrows) infiltrated by connective tissue. (Masson's trichrome technique × 110).

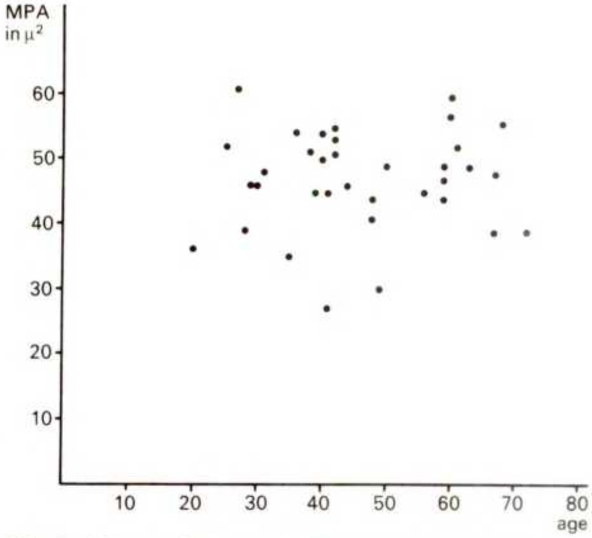

Fig. 3 Mean profile area of control detrusor smooth muscle cells compared with age.

the smooth muscle cells was $98.83 \pm 8.03\ \mu^2$. Using Student's *t* test to compare this result with the control MPA, the values were significantly different at the 1% level. Biopsy samples from the remaining two patients failed to demonstrate muscle bundles which were infiltrated with collagen. Measurement of the MPA in these two cases gave an average of $64\ \mu^2$ (Fig. 4).

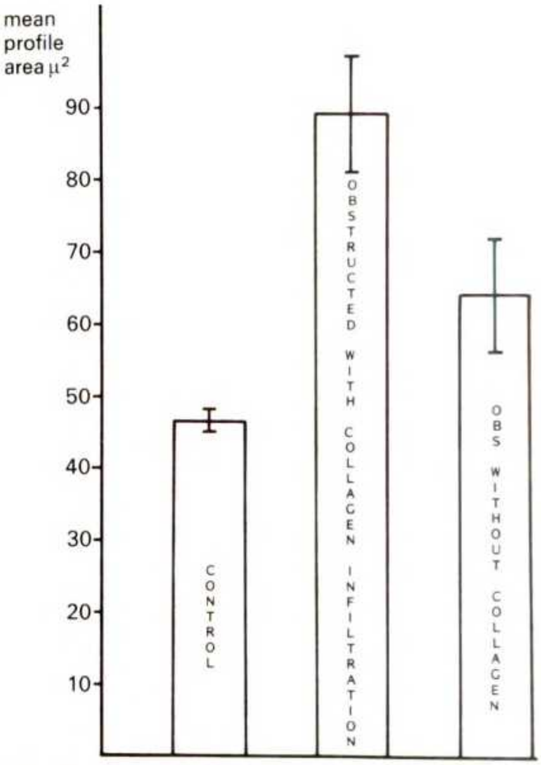

Fig. 4 Mean profile area (with standard error) of smooth muscle cells in control and obstructed patients.

2. *Measurement of cell profile diameters*

The values of cell profile diameters obtained from six control and six obstructed patients are expressed in Figure 5. The diameters from control patients ranged from 1 to 12 microns but, in contrast, 26% of the cell profile diameters in obstructed, trabeculated patients were outside this range and lay between 12 and 24 microns.

3. *Nuclear length and cell length*

Cell length was assessed using the formula suggested by Gabella (1976):

$$\text{Cell length} = \frac{\text{mean nuclear length} \times 100}{\%\ \text{nucleated cross-sectioned cell profiles}}$$

These results are expressed in the Table and the values obtained for the two groups were significantly different at the 1% level.

Discussion

In comparative morphological studies of the type described in the present report, it is essential to obtain material which can be considered to act as an adequate control. Consequently only those patients for whom bladder outflow obstruction and detrusor instability had been urodynamically and clinically excluded were deemed to provide control material. Furthermore, in all of these patients trabeculation was judged to be absent when the bladder wall was examined endoscopically and the bladder sample obtained. Histological evaluation of the tissue removed from these control patients has shown the bladder muscle bundles to be of normal appearance and devoid of connective tissue infiltration. The morphometric analysis of this smooth muscle has failed to demonstrate any significant variation in the mean profile area of the muscle cells with either age or sex.

Concerning the samples removed from a total of 14 obstructed, trabeculated bladders, 12 patients in this category had connective tissue infiltration in at least some of the biopsy material. These morphological changes were identical to those previously described by Gosling and Dixon (1980), although subjective evaluation of muscle cell size failed to reveal any evidence of hypertrophy. The quantitative data recorded in the present investigation have, however, shown a significant increase in the MPA of these cells by comparison with controls ($P < 0.01$). As suggested by Uvelius and Gabella (1980), this increase could result from artifactual or real contraction of non-hypertrophied smooth muscle cells occurring after their removal from the bladder wall of the patient. Given a constant volume of individual smooth muscle cells, if such contraction involved only a relatively short length of the cell the remainder of the fibre would possess relatively narrow diameters. On the basis of this hypothesis, measurement of actual cell diameters

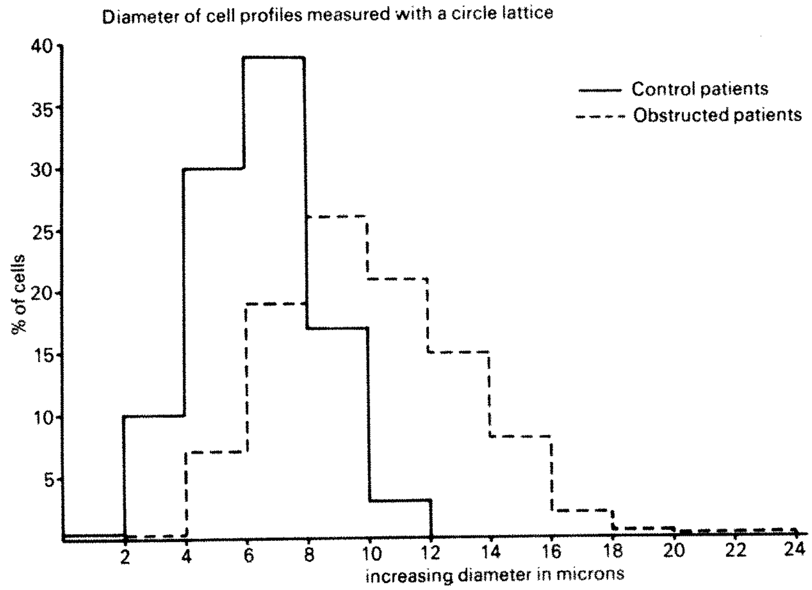

Fig. 5 Histogram of smooth muscle cell percentage and diameter in six control and six obstructed, trabeculated bladders.

would result in a bimodal distribution with the majority of fibres being less than the mean. However, it is evident from Figure 5 that the cell diameters measured in obstructed, trabeculated cases are similar to controls in having a unimodal distribution. An alternative explanation for the increase in MPA could be that non-hypertrophied cells have increased in diameter by reducing their length (*i.e.* they have contracted and become shorter and wider). To examine this hypothesis an assessment of cell length was made (Table) and the formula suggested by Gabella (1976) applied to these measurements. The results show that by comparison with controls, a significant increase ($P < 0.01$) in the mean cell length occurred in smooth muscle obtained from obstructed, trabeculated bladders. Hence it is concluded that the increase in cross-sectional MPA (occurring in the absence of changes in the proportional distribution in diameter) accompanied by an increase in cell length is due to the hypertrophy of detrusor smooth muscle cells in obstructed, trabeculated patients.

Table Cell Length and Nuclear Length in 12 Obstructed and 12 Control Patients

	Control	*Obstructed, trabeculated*
Nuclear length (μ)	22.51 ± 1.05	34.45 ± 1.45
% Nucleated profiles	18.5 ± 0.7	21.3 ± 1.3
Cell length (μ)	121.7 ± 10.7	161.7 ± 17.8

Since the biopsy material employed in the present study did not include a full thickness sample of the bladder wall, the results have not provided any direct evidence about smooth muscle hyperplasia. It is interesting to note, however, that morphological evidence of muscle cell division (*i.e.* mitotic figures) was not observed in any of the specimens examined.

Concerning the degree of cellular hypertrophy which occurs in obstructed, trabeculated bladders, the largest increase in size was observed in those patients in whom the bladder samples also showed histological evidence of connective tissue infiltration. In the two patients in whom connective tissue infiltration of bladder smooth muscle was absent, cellular hypertrophy was less marked. On the basis of this evidence it may be that the deposition of connective tissue amongst detrusor smooth muscle bundles occurs at a stage after the onset of cellular hypertrophy. Further investigation is needed in order to confirm or refute this proposal and to gain a better understanding of the functional significance of connective tissue infiltration in obstructed trabeculated bladders.

Additional work is also needed to determine the changes in the bladder wall which may occur following the relief of outflow obstruction.

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The Authors

S. A. Gilpin, MSc, Research Technician, Department of Anatomy.
J. A. Gosling, MD, Professor of Anatomy.
R. J. Barnard, FRCS, Consultant Urologist.

Requests for reprints to: J. A. Gosling, Department of Anatomy, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT.

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Exfoliative Cytology after Transurethral Resection of Superficial Bladder Tumours

F. MÜLLER, R. KRAFT and E. ZINGG

Departments of Urology and Pathology, University of Bern, Bern, Switzerland

Summary—Fifty-one patients with predominantly superficial bladder tumours underwent prospective cytological examination at predetermined intervals following surgery in order to evaluate the prognostic reliability of bladder irrigation cytology. The results suggest that positive cytology 3 days after radical transurethral resection is a reliable indicator of incomplete resection or additional occult tumour foci. The implications for post-operative management and follow-up are discussed.

The frequency of recurrence of superficial bladder tumours varies between 50 and 80%, depending on stage, grade, multichronotropism and other tumour and host characteristics (Murphy *et al.*, 1979; Soloway, 1980). In most cases recurrence develops within the first 6 to 12 months, the timing usually being in direct proportion to the malignancy (grading) of the tumour. It is difficult to distinguish between true recurrence and incomplete resection of the tumour, particularly since at the time of appearance of the tumour the endoscopically inconspicuous urothelium contains a high proportion of multifocal, histologically and cytologically abnormal areas in the form of atypical papillary hyperplasia, dysplasia and carcinoma *in situ* (Soloway *et al.*, 1978; Murphy *et al.*, 1979; Soloway and Masters, 1980; Felderhof *et al.*, 1983). According to Heney *et al.* (1978), such abnormalities are found in 77% of patients with high grade tumours and 15% of those with low grade tumours.

So far no reliable method has been devised to confirm total ablation of the bladder tumour following what appears macroscopically to be complete transurethral resection.

We carried out cytological examinations at predetermined intervals following surgery in order to determine the reliability of bladder irrigation cytology in assessing urothelial malignancy. We also tried to ascertain whether the information thus gained could help to decide the frequency of follow-up and whether further treatment, such as additional transurethral resection or topical chemotherapy, was required.

Patients and Methods

Fifty-one patients with papillary bladder tumours underwent transurethral resection. In each case an experienced surgeon confirmed that the resection was complete and that it extended into healthy tissue. Details of tumour stage and grade are shown in Table 1.

Table 1 Bladder Tumour According to Stage and Grade (n = 51)

Stage	35 Ta	14 T1	1 T2	1 T3
Grade	3 G1	24 G2	24 G3	

Immediately after TUR and again 3 days later, at removal of the catheter, the fluid collected during bladder irrigation was examined cytologically. The material was obtained by vigorous irrigation of the bladder with 60 ml isotonic saline for 1 min. The examinations were carried out by the same pathologist who, in a previous series of cytological

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examinations of bladder irrigation fluid, had attained a sensitivity of 84.5% and a specificity of 98.5%. The first follow-up examination, with cystoscopy and cytology, was carried out after 3 to 6 months.

Results

In 17 of 51 cases (33.3%) tumour cells were found in the irrigation fluid obtained immediately after tumour resection, but their viability could not be reliably assessed because the material showed signs of severe mechanical and thermoelectrical damage (Fig. 1).

In 12 cases (23.5%), examination of the bladder irrigation fluid 3 days after electroresection revealed tumour cells whose morphology could be classified unequivocally (Table 2, Figs 2 and 3). In nine cases (17.6%), cytological examination 3 to 6 months post-operatively revealed tumour cells and a papillary tumour was found on endoscopy (Figs 4 and 5).

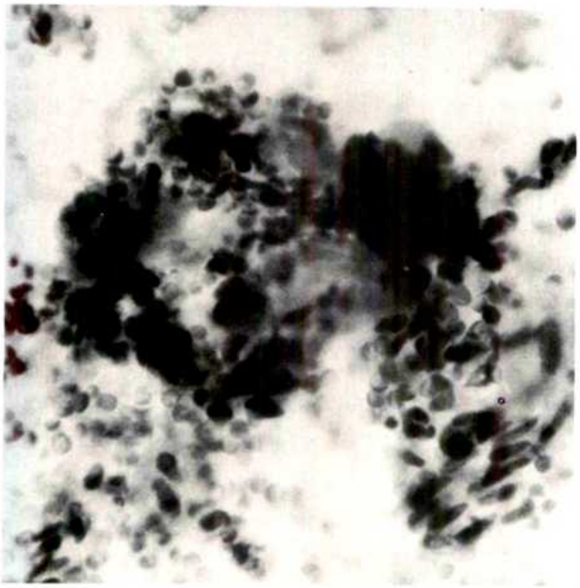

Fig. 1 Cytology immediately after TUR shows groups of urothelial cells with nuclear layering (indicating mechanical damage), absence of chromatin structure as a result of thermal injury, and herring-bone pattern orientation of the nuclei caused by electric current (Papanicolaou × 563).

Table 2 Results of Early Cytological Controls

Exfoliative cytology *n = 51*	*Immediately after TUR*	*3 days after TUR*
Positive	17	12
Negative	34	39

In three cases with false positive exfoliate cytology initially, the findings could not be confirmed

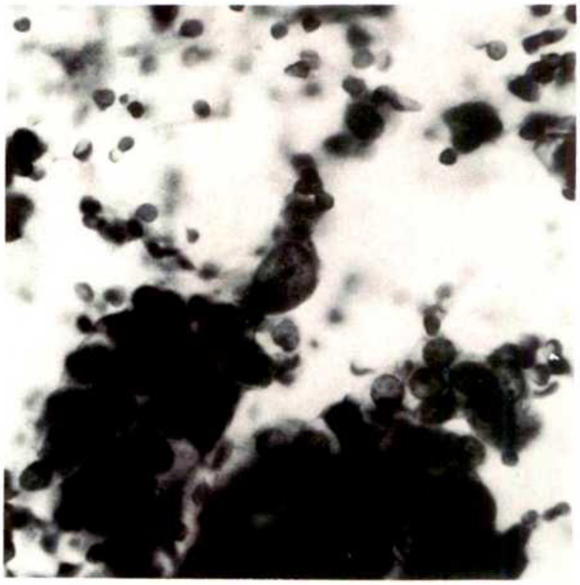

Fig. 2 Cytology 3 days after TUR shows intact groups of urothelial carcinoma cells, variation in the sizes of the nuclei, coarsely granular chromatin structure with clearly visible nucleoli, and an increase in the nucleoplasmic ratio (Papanicolaou × 563).

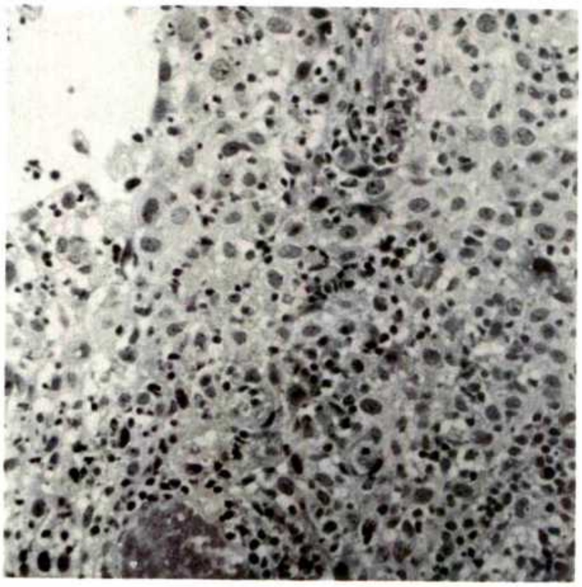

Fig. 3 Tissue subsequently resected from same patient as in Figure 2. Remnants of an invasive solid urothelial carcinoma with infiltration of the lamina propria can be seen, with variation in the size and structure of the cell nuclei and eosinophilic and lymphocytic infiltration (T2, G2-3) H and E × 221).

at follow-up. One patient received systemic chemotherapy for pulmonary metastases, the second was given adjuvant treatment with etretinate (vitamin A acid), and the third underwent cutaneous and topical immunostimulation with BCG in a controlled trial.

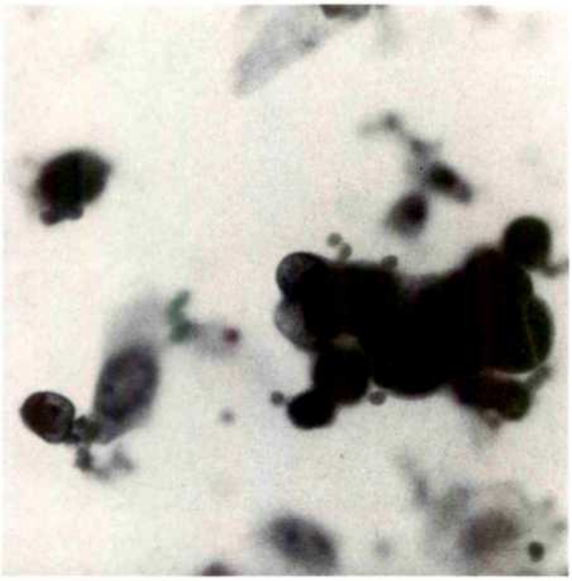

Fig. 4 Cytology 6 months after TUR showing groups of urothelial carcinoma cells, coarsely granular chromatin structure with some of the nucleoli clearly visible, and scanty cytoplasm (carcinoma cell type) (Papanicolaou × 563).

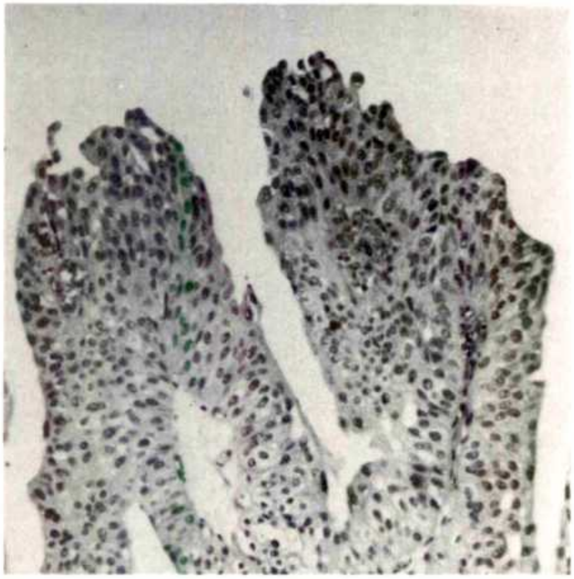

Fig. 5 Tissue subsequently resected from same patient as in Figure 4 showing papillary carcinoma at another site growing into the lamina propria (T2, G2) (H and E × 140).

Of 39 patients (76.4%) with negative cytology on the third post-operative day, 29 (56.8%) were cytologically and cystoscopically tumour-free at initial follow-up 3 to 6 months later. In 10 patients (19.6%) the cytology had become positive at follow-up, and at the initial follow-up or later a recurrence of tumour was confirmed endoscopically (Table 3).

Table 3 Results of Cytological Follow-up

Exfoliative cytology 3 days after TUR	*3-6 months after TUR*	*n 51*	*% 100*
Positive	Positive	9	17.6
Positive	Negative	3	5.8
		12	23.5
Negative	Negative	29	56.8
Negative	Positive	10	19.6
		39	76.4

Discussion

Transurethral resection of a superficial bladder tumour should be followed by an objective assessment of the completeness of resection. Histological examination of the resected tumour tissue permits staging (T) and grading (G) of the tumour, so that on the basis of previous experience a statistical estimate of the risk of progression and recurrence can be made (Heney *et al.*, 1983). However, this reveals nothing about macroscopically inconspicuous changes in the remaining urothelium (residual tumour, papillary hyperplasia, urothelial dysplasia and carcinoma *in situ*) and their neoplastic potential. Neither endoscopy, biopsy nor cytology can, on their own, provide all of the necessary prognostic information (Loening *et al.*, 1978). At present there is no sensitive and specific indicator (Whitmore 1984).

Urinary cytology is becoming widely accepted as a diagnostic and follow-up procedure in cases of bladder cancer (Morrison *et al.*, 1984; Murphy *et al.*, 1984). It permits early detection of endoscopically and histologically inconspicuous tumours and urothelial changes such as latent carcinoma *in situ*. Carcinoma may be cytologically detectable months or years before it becomes endoscopically or histologically visible (Murphy, 1977; Murphy *et al.*, 1979; Studer *et al.*, 1982). In addition, cytology permits differentiation between inflammatory changes and neoplastic lesions. In assessing the value of cytological examination the disadvantages of the method and any sources of error must be taken into account. Sensitivity and specificity are largely determined by technical factors (*e.g.* the manner in which the specimen is obtained and processed) but they also depend upon the experience of the cytologist. If a tumour is present the chances of detecting it (*i.e.* the sensitivity of the method) can be increased by repeating the cytological examination, especially in the case of low grade tumours whose cells are morphologically similar to those of normal urothelium (Allegra *et al.*, 1966, 1972; Cox and Friedell, 1977; Gamarra and Zein, 1984; Murphy *et al.*, 1984). Intravesically instilled chemotherapeutic agents, particularly alkylating substances such as thiotepa or mitomycin C, may cause cytotoxic artefacts and thereby increase the difficulty of cytological assessment (Murphy *et al.*, 1981). Nevertheless, according to Murphy *et al.* (1984), the histological and cytological diagnoses agree in 92% of cases.

In 33.3% of patients, cytological examination of the irrigation fluid obtained immediately after electroresection of a bladder tumour reveals tumour cells, but artefacts prevent a reliable assessment of their viability. It is not known whether tumour cells which remain in the bladder following electroresection can become implanted in the superficially damaged tissues and thus cause recurrence at the resection site, as has been suggested by Wallace and Hershfield (1958) and Soloway and Masters (1980). The possibility that this might occur is an argument in favour of early topical chemotherapy by instillation of an alkylating agent immediately after transurethral resection (Felderhof *et al.*, 1983). In future the cytological findings may become an important determinant of the necessity for such post-operative therapy.

However, cytological assessment of specimens obtained by immediate post-operative bladder irrigation is not without problems and may give false positive results. Of 17 cases, only 12 were still positive 3 days after the operation and only nine were positive at the 6-monthly follow-up. We therefore feel that the immediate post-operative cytological check as used, for example, by Zincke *et al.* (1984) in a prospective trial, is less informative than that carried out 2 to 3 days later. Three days after macroscopically radical TUR, viable tumour cells were still cytologically detectable in 23.5% of cases. These early positive findings suggest that either the resection was incomplete, that papillary tumours had been overlooked or that there were latent areas of carcinoma *in situ*. Orandi and Orandi (1976) carried out cytological examination as a 2-monthly screening procedure following transurethral resection of superficial bladder tumours but did not perform the first examination until 2 months after the operation.

Whatever the method, the aim of treatment is eradication of the tumour with retention of normal bladder function. A prerequisite of successful management is early recognition of tumour recurrence and its progression to higher T and G levels (Lutzeyer *et al.*, 1982). The presence of mucosal anomalies (atypical epithelium and carcinoma *in situ*) associated with low stage, low grade tumours seems to herald muscular infiltration by recurrent tumour (Cummings, 1980) and suggests that more radical and aggressive therapy may be indicated.

Although it is too early to draw definite conclusions from this preliminary report, we feel that the following observations can be made. Routine cytological investigation of the bladder irrigation fluid after transurethral tumour resection provides useful information about the neoplastic potential of the urothelium. It complements the other well known tumour characteristics (stage, grade, multichronotropism, number and sequence of recurrences) in helping to establish the prognosis. The main advantage of the method is that it permits detection of tumours at a very early stage, frequently before they are revealed by other investigations.

Positive cytology shortly after the operation (*e.g.* 3 days) is a reliable indicator of incomplete resection or of additional, latent tumour foci. Such patients require intensive follow-up or local chemotherapy, since recurrence of the tumour is inevitable. Cytological follow-up 3 to 6 months after TUR complements endoscopy as a procedure for the detection of early recurrence or second tumours.

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The Authors

F. Müller, MD, Assistant, Department of Urology.

R. Kraft, MD, Head of Division of Cytology, Department of Pathology.

E. Zingg, MD, Professor and Director, Department of Urology.

Requests for reprints to: F. Müller, Department of Urology, University Hospital, 3010 Bern, Switzerland.

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Urethral Dysplasia and Bladder Cancer in Cystectomy Specimens

A. G. COUTTS, K. M. GRIGOR and J. W. FOWLER

Department of Urology, Royal Infirmary and Department of Pathology, University of Edinburgh, Edinburgh

Summary—Sixty-five patients had a cystectomy for a solitary bladder tumour (28) or multifocal lesions (37). The histological extent of the disease within the bladder was correlated with mucosal abnormalities within the urethra. The presence of multifocal or solitary bladder disease was not an accurate predictor of the presence or absence of urethral dysplasia. Details of mortality and morbidity associated with one-stage cysto-urethrectomy are presented and it is concluded that irrespective of whether the bladder contains a solitary or multifocal tumour, complete cysto-urethrectomy should be considered as the treatment of choice whenever cystectomy for attempted cure is indicated.

Surgical removal of the bladder remains the treatment of choice for uncontrollable superficial transitional cell carcinoma or recurrence following radiotherapy. Opinion is divided as to how extensive the removal of the lower urinary tract urothelium should be. Some surgeons carry out cysto-urethrectomy routinely on all patients (Schellhammer and Whitmore, 1976), whilst others feel that cysto-prostatectomy in the male and cystectomy with urethral removal in the female is adequate where the bladder tumour is solitary. They believe that careful monitoring of the anterior urethral cytology may avoid the necessity of extending the operation, thereby perhaps increasing mortality and/or morbidity (Skinner *et al.*, 1980).

Following the report by Hendry *et al.* (1974), it has been our policy to carry out radical cysto-urethrectomy in all patients requiring cystectomy other than as a palliative procedure.

Careful histological study of the excised tissue, with regard to the extent of bladder and urethral changes, has been carried out to see whether this policy is justified in those patients with solitary as well as those with multifocal carcinoma of the bladder. Whilst extensive or full ablation of lower urothelium may be theoretically desirable, it would not be justified if there were significantly greater morbidity and/or mortality; data on operative mortality and morbidity accompanying the radical procedure in our series are therefore presented.

Materials and Methods

In the years 1974 to 1983, 65 patients had a cystectomy carried out by the senior author (JWF); there were 47 male and 18 female patients with an average age of 62.5 years (range 42-79). Fifty-six patients, 39 male and 17 female, underwent radical cysto-urethrectomy as an attempted cure. Nine patients, eight male and one female, had simple cystectomy as a palliative procedure.

Those patients presenting with multifocal tumours had various forms of primary therapy before cystectomy, thereby significantly prolonging the time interval between first diagnosis of bladder cancer and definitive cystectomy to an average of 25 months (range 1-150) compared with 7.4 months (range 1-56) for those with a solitary tumour.

The main indications for cystectomy in 35 patients were uncontrolled multifocal disease and large bulk of tumour (base greater than 6 cm in diameter). A further 27 patients had a cystectomy

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because of recurrence after radical radiotherapy, and three patients had a palliative cystectomy with no other treatment. Almost two-thirds of patients with solid tumours and almost one-third of those with multifocal lesions had primary cystectomy with or without pre-operative radiotherapy.

Operative Technique

Bowel preparation by both antibiotic (neomycin and metronidazole) and mechanical means was undertaken pre-operatively. The prophylactic antibiotics, flucloxacillin, metronidazole and gentamycin, were given for 5 days post-operatively. In male patients the radical operation consisted of cysto-prostato-urethrectomy *en bloc*, plus removal of internal iliac, obturator and common iliac lymph nodes. The distal para-aortic lymph nodes were sampled but not cleared. Anterior pelvic clearance plus similar lymphadenectomy was performed in females. Ileal loop diversion was performed in all but one patient who had a ureterocolic diversion.

A detailed histological study of bladder and urethra was carried out to ascertain the exact extent of malignant and pre-malignant change. An analysis of the operative mortality and morbidity associated with the radical procedure is presented.

Histological techniques

In the early part of the survey, the excised bladder was fixed for histological assessment by simple immersion in formalin (4% neutral buffered formaldehyde in saline), but this resulted in poor fixation of the inner parts of the specimen, including the urothelium of the bladder and urethra. Improved fixation has since been achieved by inflating the fresh specimen with formalin immediately after surgical removal and before total immersion in fixative. When totally fixed, blocks for histological examination were taken as follows:

(i) The bladder tumour, or tumours if multifocal.
(ii) Random mucosal biopsies from different quadrants at sites free from macroscopic tumour.
(iii) The distal portions of ureters attached to the bladder.
(iv) The prostatic urethra and surrounding prostate.
(v) The urethra immediately distal to the membranous portion.
(vi) The mid-penile urethra.
(vii) The distal urethra.

In the female the urethra was sampled *in toto*.

Tumours were regarded as multifocal when more than two distinct frank carcinomas were present in addition to the main tumour. The tumours were graded and staged histologically according to the UICC (1978) guidelines, incorporating the subdivisions of pT1 and pT3 as discussed by Chisholm *et al*. (1978).

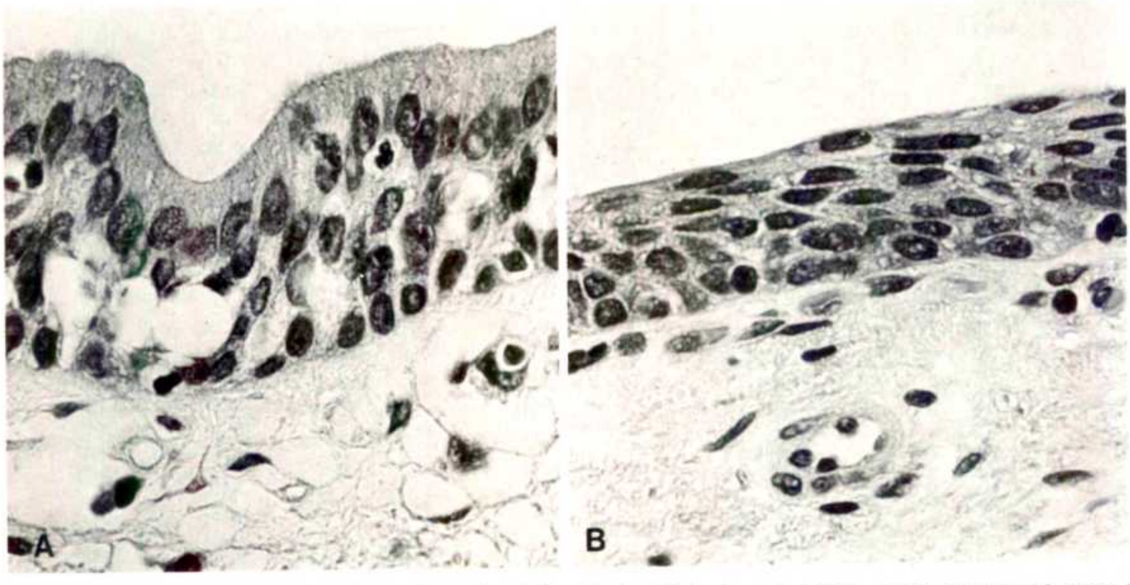

Fig. 1 Mild urethral dysplasia. The male anterior urethra is lined by stratified columnar epithelium (Fig. 1A: normal mucosa) or transitional epithelium. Figure 1B shows mild dysplasia with loss of cellular polarity at the base but good maturation to flattened transitional cells at the surface. (H and E × 640).

Paraffin sections stained by haematoxylin and eosin were examined for the presence or absence of frank tumour, carcinoma *in situ* (CIS) or dysplastic change by one author (KMG). Urethral dysplasia, when present, was graded as mild (Fig. 1), moderate (Fig. 2) or severe (Fig. 3); 46 complete urethras were suitable for study, 33 male and 13 female. A further 10 prostatic urethras were available from those patients who had simple cysto-prostatectomy, or from cysto-urethrectomy specimens where the penile urethra was not assessable.

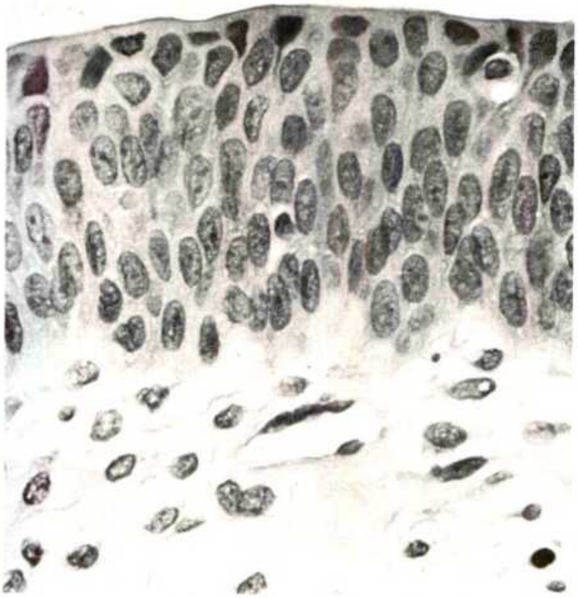

Fig. 2 Moderate urethral dysplasia. The transitional epithelium is thickened and the loss of polarity extends further up towards the surface. (H and E × 640).

Results

The histological characteristics of the bladder carcinomas, whether solitary or multifocal, are shown in Tables 1 and 2. Twenty-eight specimens contained solitary tumours: 22 of these (79%) were poorly differentiated with grade 3 (G3) histology, and 20 (71%) had invaded at least into deep muscle of the bladder wall (pT3 and pT4). Multifocal tumours were present in 37 specimens and, as might be expected in uncontrollable disease, most of these were assessed as G3 (21 cases, 57%) or G2

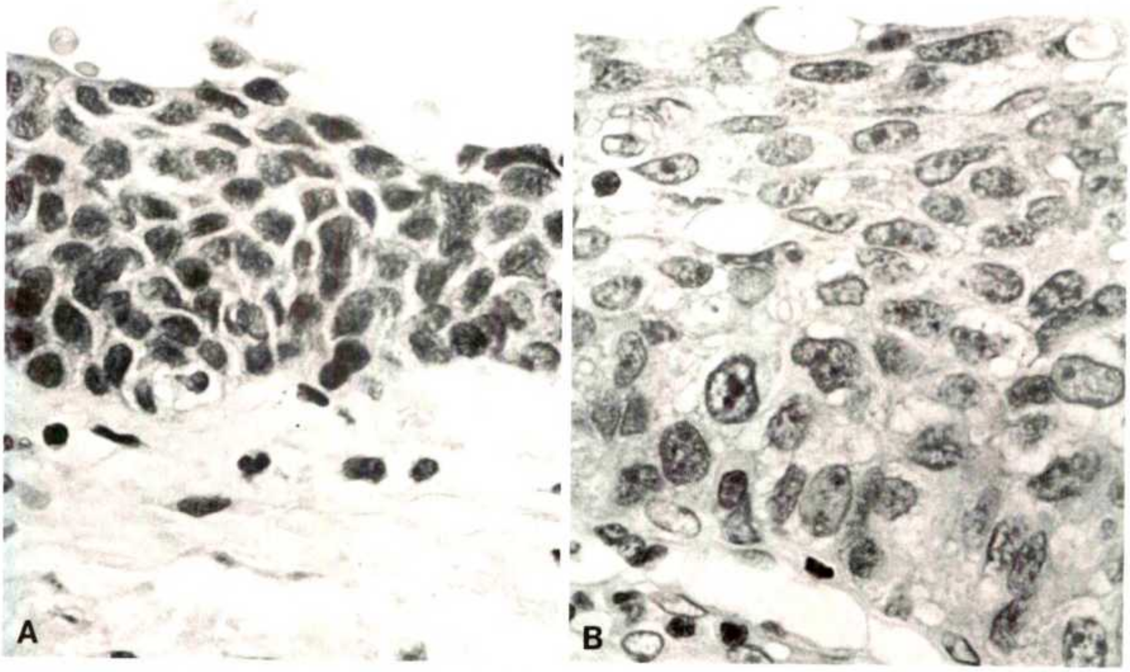

Fig. 3 A. Severe urethral dysplasia. The loss of polarity is almost full thickness with only very superficial maturation. B. Carcinoma *in situ*. The dysplastic cells extend to the surface of the mucosa. (H and E × 640).

(11 cases, 30%). The remaining patients with multifocal disease had complete resolution of tumours following pre-operative radiotherapy or endoscopic ablation (4 patients), or histologically unassessable tumour due to radionecrosis (1 patient).

Table 1 Histological Grade and Stage (UICC, 1978) of Tumour in 28 Patients Treated by Cystectomy for Solitary Bladder Carcinoma

Tumour stage	*Histological grade* *G1*	*G2*	*G3*	*Total*
pT0	—	—	—	1*
pT1a	—	—	1	1
pT1b	—	2	1	3
pT2	—	1	2	3
pT3a	—	1	4	5
pT3b	—	1	12†	13
pT4	—	—	2‡	2
Total	0	5	22	28

* G3pT2 tumour which regressed completely with pre-cystectomy radiotherapy.

† Includes one poorly differentiated squamous cell carcinoma.

‡ Two poorly differentiated squamous cell carcinomas.

Table 2 Histological Grade and Stage (UICC, 1978) of Tumour in 37 Patients Treated by Cystectomy for Multifocal Bladder Carcinoma

Tumour stage	*Histological grade* *G1*	*G2*	*G3*	*GX*	*Total*
pT0	—	—	—	—	4*
pTIS	—	—	3	—	3
pTa	—	1	—	—	1
PT1a	—	3	1	—	4
pT1b	—	1	1	—	2
pT2	—	2	6	—	8
pT3a	—	1	3	—	4
pT3b	—	1	2	—	3
pT4	—	2	5	—	7
pTx	—	—	—	1†	1
Total	0	11	21	1	37

* Three patients had pre-cystectomy radiotherapy and no evidence of tumour in resected specimen.

Pre-irradiation tumours were:

(i) G2pT2.

(ii) multiple G1pTa.

(iii) clinically stage 2. No histology available.

One patient had multiple widespread recurrence of G2pTa: all tumour was removed endoscopically prior to cystectomy.

† G2pT2 tumour treated with radiotherapy. Necrotic tumour only found at cystectomy.

Histology

Random block bladder

The random sections taken at a distance from tumour through macroscopically normal mucosa showed dysplasia or carcinoma *in situ* in 39% of patients with a solitary tumour and in 73% of those with multifocal lesions (Table 3).

Prostatic urethra

Forty-three prostatic urethras were suitable for examination, 21 (49%) showing no abnormality, frank carcinoma being present in 4 (9.3%), carcinoma *in situ* in 6 (14%) and dysplasia in 12 (28%). These changes were observed in the lining mucosa of the prostatic urethra and in the ducts and acini of the periurethral glands. Sometimes the glands and not the adjacent surface mucosa (or *vice versa*) were affected. When the random block bladder section was normal, normal urethral epithelium was present in 89%. When carcinoma *in situ* or dysplasia was found in the bladder, 80% of patients showed either CIS or dysplasia in the urothelium of the prostatic urethra (Table 4). This degree of pre-

Table 3 Histology of Random Blocks of Bladder from 65 Cystectomy Specimens with Solitary or Multifocal Carcinoma

Histology of random bladder blocks	*Indication for cystectomy* *Solitary tumour Number of cases*	*multifocal tumour Number of cases*
Normal epithelium	17 (61%)	10 (27%)
Dysplasia	6 (21%)	12 (32%)
CIS	5 (18%)	15 (41%)
Total	28	37

Table 4 Correlation of Histology in Random Block of Bladder with Histology of Prostatic Urethra in 43 Male Cystectomy Cases

Histology of prostatic urethra	*Histology of random block of bladder* *Normal epithelium*	*Dysplasia/CIS*	*Total*
Normal epithelium	16 (89%)	5 (20%)	21
Dysplasia	1	11	12
CIS	1 (11%)	5 (80%)	6
Frank carcinoma	0	4	4
Total	18	25	43

diction occurred irrespective of whether the bladder was the seat of macroscopically solitary or multifocal tumour.

Anterior urethra

Due to faulty fixation or loss of tissue, only 33 male anterior urethras and 13 female urethras were available for study, giving a total of 46 suitable for analysis. Twenty of these showed either dysplasia or CIS. A comparison of random bladder sections with the histological findings in the anterior urethra is shown in Table 5. When the bladder biopsy showed no urothelial abnormality (22 patients), the corresponding urethral mucosa was similarly free of disease in most of them (19), with only three displaying urethral change. When dysplasia or CIS was seen in the random bladder biopsy (24 cases), similar changes were usually present in the urethra (17) and only seven individuals had no urethral abnormality. As can be seen from Table 5, random block bladder biopsy was a more accurate predictor of the presence or absence of urethral disease than the macroscopic presence or absence of multiple tumours.

Table 5 Factors Useful in Predicting Anterior Urethral Dysplasia or CIS in 46 Patients (33 Male, 13 Female) Treated by Cystectomy for Bladder Carcinoma

(a) Correlation of urethral abnormality with histology of random bladder block

	Histology of anterior urethra		
Histology of random block of bladder	*No mucosal abnormality*	*Mucosal dysplasia or CIS*	*Total*
No mucosal abnormality	19 (86%)	3 (14%)	22
Mucosal dysplasia or CIS	7 (29%)	17 (71%)	24
Total	26	20	46

(b) Correlation of urethral abnormality with multiplicity of bladder tumours

	Histology of anterior urethra		
Indication for cystectomy	*No mucosal abnormality*	*Mucosal dysplasia or CIS*	*Total*
Solitary tumour	16 (71%)	5 (29%)	21
Multifocal tumours	10 (40%)	15 (60%)	25
Total	26	20	46

Male anterior urethra

Varying degrees of CIS/dysplasia were found in 14/33 (42%) of urethras distal to the membrane. Table 6 shows the changes in the 14 urethras at the three sites. It was apparent that changes were as common distally as proximally and that, when present, were extensively found within the urethra. Also, it was possible to have a normal proximal urethra with distal mucosal change.

Female urethra

Six of 13 female urethras showed dysplasia, three moderate and three severe. We felt it impracticable to divide the findings into pre- and post-membrane in this group.

Mortality and morbidity

One male patient aged 74 with T3b squamous carcinoma underwent palliative simple cystectomy. Wound dehiscence developing at 1 week was resutured. One week later he died of severe haematemesis, which could not be controlled, due to a stress ulcer in the second part of the duodenum. This was the only direct operative death among 65 patients.

There were no operative deaths in the radical cystourethrectomy group (56 patients). One female patient in this series, having had an anterior exenteration, died 3 months later without leaving hospital. Post-operatively, following wound dehiscence which was clinically unrecognised because of gross obesity but was re-sutured, she developed an entero-cutaneous fistula secondary to a Richter hernia which was treated conservatively. This settled over the 3-month period and discharge was planned, but hypercalcaemia secondary to bony metastases developed. Bone scan immediately prior to surgery had been negative, and she died from progression of the disease.

Table 6 Site and Severity of Dysplasia in 14 Male Patients with Mucosal Abnormality in the Urethra Distal to the Membrane

	Anterior urethra distal to membrane		
Degree of dysplasia	*Proximal*	*Mid*	*Distal*
Carcinoma *in situ* or severe dysplasia	3	3	2
Moderate dysplasia	9	9	8
Mild dysplasia	1	0	1
No mucosal abnormality	1	2	3
Total	14	14	14

The complications of the operations are shown in Table 7. Thirteen patients, five of whom presented with plumonary emboli, had venographically proven deep venous thrombosis. Post-operative rates of abdominal wound infection, dehiscence and other standard complications are similar to those reported by Skinner *et al.* (1980) and Thomas and Riddle (1982). Three patients had significant post-operative haemorrhage, one of whom required re-operation due to continued bleeding from the retropubic veins. Only one patient had a proven septicaemia and there were no cases of renal failure. Three patients had significant uretero-ileal urinary leaks and one of these required immediate re-exploration and suture. One female patient progressed to an established uretero-cutaneous fistula via the perineal wound and required delayed formal excision. One patient developed rectosigmoid large bowel pseudo-obstruction and required a proximal colostomy. No cause for this was found, but he had had pre-operative radiotherapy which was probably contributory. The colostomy was closed at 3 months. Perineal wound complications were few, *viz.* the fistula mentioned above and three patients with superficial wound infections which all settled spontaneously.

Table 7 Post-Operative Complications in 56 Patients Undergoing Radical Cysto-urethrectomy

Complications	*Number of patients*
Pulmonary collapse/pneumonia	4 (7%)
Pulmonary embolism	5 (9%)
Deep venous thrombosis	13 (23%)
Wound infection	5 (9%)
Peripheral wound infection	4 (7%)
Perineal fistula	1 (2%)
Prolonged ileus	7 (13%)
Large bowel obstruction	1 (2%)
Haemorrhage	3 (5%)
Septicaemia	1 (2%)
Uretero-ileal leak	3 (5%)
Enterocutaneous fistula	1 (2%)

Survival

Actuarial survival curves have been constructed for all 65 patients. The 5-year survival rate for those presenting with multiple tumours was 65%, and 35% for those with solitary tumours. This difference was not significant ($P=0.056$, Lee-Dense Test), and a longer period will have to elapse before it is possible to analyse the survival data with reference to the relevance of urethral histology.

Discussion

Curative cystectomy for locally uncontrollable bladder cancer requires the removal of all potentially involved urothelium. The argument of whether a local cystectomy or a total cysto-urethrectomy should be done has been pursued in two directions: firstly, the need for urethrectomy in the face of an apparently solitary bladder tumour and, secondly, the fear that the extra procedure may add significantly to the post-operative morbidity and mortality. This study emphasises the fact that uncontrolled bladder cancer tends to be multifocal, at least microscopically if not macroscopically. Eleven of 28 patients with solitary tumours had CIS or dysplasia in macroscopically normal mucosa and those, together with the 37 patients with overt multifocal tumours, gave a total of 48 of 65 patients with multifocal disease. Using the finding of a solitary tumour as an indication of the absence of urethral disease was incorrect in 30% of cases. When the "normal" bladder mucosa was also histologically negative, the error was reduced to 20%. The histological study has not only confirmed the higher risk of urothelial disease in overt multifocal carcinoma, but also emphasises the incidence of urethral dysplasia accompanying solitary bladder lesions. These findings corroborate the report of Hendry *et al.* (1974).

Urethral tumour recurrence within the isolated anterior urethra has been estimated as being between 4 and 18% of patients following simple cystectomy for bladder cancer (Gowing, 1960; Cordonnier and Spjut, 1962; Schellhammer and Whitmore, 1976) and carries a uniformly bad prognosis. Furthermore, delayed urethrectomy has a significant incidence of perineal recurrence and inguinal lymph node involvement, but this is avoided by simultaneous urethrectomy (Schellhammer and Whitmore, 1976). The true incidence of urothelial recurrences is unknown; those appearing at the resection line at the membrane must often be classified as local intrapelvic recurrence and are uncontrollable.

One post-operative death occurred in this series and one patient died of progression of disease before leaving hospital because of post-operative complications. Morbidity was in general similar to that reported for simple cystectomy, although the incidence of deep venous thrombosis (DVT) was the one exception, occurring in 13/56 patients within the radical operative group, with an embolus rate of 4/56. The high recorded DVT rate may be explained by the unit's policy of venography on suspicion, but the embolus rate is higher than that reported in much larger series (Vinnicombe and Abercrombie (1978), 3/99 patients; Skinner *et al.* (1980), 1/100 patients; Thomas and Riddle (1982), 3/100 patients). Prophylaxis of DVT consisted of elasticated support stockings pre- and post-operatively, and pneumatic socks during the operation. On these figures there is a strong case to be made for prophylactic anticoagulation as advocated by Skinner *et al.* (1980), despite the risk of post-operative haemorrhage. Great care must be taken in trying to correlate operative mortality and morbidity in this small series with those larger series quoted, but at present the mortality and morbidity rates follow the improving trend reported therein. Where urethrectomy is not carried out the patient requires regular review by cytology and endoscopy, and has both the worry concerning recurrent cancer and the 14% chance of requiring further surgery; thus the pre-operative anxiety state is not ameliorated by the operation, nor does the patient have the consolation of normal urinary function.

It is concluded that a simultaneous urethrectomy with cystectomy can be accomplished with little or no increase in mortality or morbidity. Since urethral dysplasia or carcinoma *in situ* often accompanies bladder cancer, we recommend the extended operation in all patients where cure is being attempted.

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The Authors

A. G. Coutts, FRCSE, Registrar in Urology, Royal Infirmary of Edinburgh.

K. M. Grigor, BSc, MD, MRCPath, Senior Lecturer in Pathology, University of Edinburgh.

J. W. Fowler, FRCSE, Consultant Urologist, Royal Infirmary of Edinburgh.

Requests for reprints to: J. W. Fowler, Department of Urology, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW.

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Plasma Hormone Levels in Patients with Prostatic Carcinoma Treated with Diethylstilboestrol and Estramustine

M. C. BISHOP, C. SELBY and M. TAYLOR

Departments of Urology and Clinical Chemistry, City Hospital, Nottingham

Summary—Plasma testosterone, oestradiol, luteinising hormone (LH) growth hormone and prolactin were measured serially in 140 patients with advanced prostatic carcinoma (T3, T4, MI and MO) randomised in a trial of diethylstilboestrol 3 mg/day against estramustine 560 mg/day. Both drugs suppressed plasma testosterone and LH and increased plasma growth hormone and prolactin, though estramustine induced a greater rise in prolactin. Oestradiol levels fell on stilboestrol but were considerably elevated on estramustine. Initial hormone levels reflected neither the extent of disease nor the response to treatment. The data also showed that close attention should be given to plasma LH in identifying patients who are unreliable, since intermittent hormone dosage caused an exaggerated rise even when plasma testosterone remained at castrate levels.

The dependence of specific receptors in prostatic tissue on gonadotrophins and sex hormones must be influential in the natural history of prostatic cancer and its response to therapy (Ekman *et al.*, 1979; Harper and Griffiths, 1982; Sandberg and Karr, 1983). It has been suggested that certain hormone profiles could define particular groups of patients and it has also been shown that different forms of treatment induced characteristic changes in plasma hormone levels (Harper *et al.*, 1976; Bartsch *et al.*, 1977; British Prostate Group, 1979). Several hormone estimations were therefore included in the protocol of the prospective trial of two oestrogen preparations in the the treatment of advanced prostatic cancer. The purpose of these measurements was to see if the benefit of one or other drug could be related to specific hormone changes.

Patients and Methods

One hundred and forty patients (mean age 72 years, range 56-86) with T3 or T4 carcinoma of the prostate were randomised in a trial of diethylstilboestrol (DES) 3 mg/day against estramustine (Estracyt (ES)) 560 mg/day. A crossover arm was included. Patients were ambulant and not on treatment with drugs known to affect prolactin secretion (*e.g.* phenothiazines, methyl dopa, metaclopramide) other than the sex hormone therapy itself. All blood samples were taken between 2 and 4 pm.

Approximately 50% of patients had bone metastases at presentation, identified and subsequently assessed by serial radionuclide bone scanning (99m Tc diphosphate). The progress of skeletal metastases on hormone treatment and the extent of initial metastatic disease were graded simply (Table 2). The biochemical assessment of disease status is the subject of another publication but serial plasma alkaline and acid phosphatase levels are quoted here in relation to hormonal changes in one patient. Data were analysed after log transformation. Student's *t* test was used to test significance.

The measurement of all hormones was performed by radioimmunoassay (RIA). Testosterone and oestradiol were extracted from plasma using diethyl ether. Duplicate aliquots of the ether were evaporated to dryness, the residue dissolved in

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0.1 M phosphate buffer pH7.4 containing 0.1% gelatin. The immunoassay was performed on these extracts. Testosterone was measured using an antibody (purchased from Steranti Research Ltd) raised against a testosterone-3 conjugate, with tritiated testosterone (purchased from Amersham International) as the label.

Antibody bound and free fractions were separated using dextran coated charcoal and the radioactivity in the antibody bound fraction counted in an LKB 81000 Liquid Scintillation counter. The sensitivity of the method was 2 nmol/l, the recovery of added testosterone 98% and the antiserum showed no detectable cross reactivity with estramustine or diethylstilboestrol.

Oestradiol was measured similarly using an antibody (also obtained from Steranti) raised against an oestradiol-6-carboxymethyl oxime conjugate, and using tritium labelled oestradiol (Amersham International). Separation of antibody bound fraction and counting conditions were similar to those used for testosterone. The sensitivity of the assay was 40 pmol/l, recovery of added oestradiol 92% and the antiserum showed more than 100% cross reactivity with estramustine and less than 1% with diethylstilboestrol. Prolactin and luteinising hormone were both measured using reagent kits purchased from CIS (UK) Ltd, and the procedure performed according to the manufacturer's instructions. The sensitivity of the prolactin assay was 30 mU/l and LH 1 mU/l. Growth hormone was estimated by the procedure recommended by the MRC Immunoassay Team, Edinburgh, and using reagents supplied by them. The sensitivity of the assay was 0.5 mU/l.

No separate estimations of specificity or recovery were performed for these assays. The normal reference ranges of the assays were:

Testosterone	: 8-28 nmol/l
Oestradiol	: Up to 220 pmol/l
LH	: 0.3-12 mU/l
Prolactin	: 100-700 mU/l
Growth hormone	: Up to 10 mU/l

Results

Pre-treatment

The results of the five different hormone assays are shown in Table 1. Plasma testosterone was in the normal range in the majority of patients. In some cases, plasma oestradiol levels were above the up-

Table 1 Mean Plasma Hormone Levels in Patients with (MI) and without (MO) Metastases on Treatment (ES and DES)

		DES *Before treatment*		*On treatment*		*Estracyt* *Before treatment*		*On treatment*	
		MO	*MI*	*MO*	*MI*	*MO*	*MI*	*MO*	*MI*
Testosterone	x	15.9	12.8	1.8	1.9	17.4	13.4	1.8	1.9
nmol/l	s	7.6	4.7	0.6	0.6	7.3	7.4	0.4	0.6
	n	23	18	23	24	22	19	17	27
Oestradiol	x	216.7	118.4	61.0	61.0	186.4	143.2	4000	4000
pmol/l	s	121.6	60.4	17.3	32.6	85.7	67.7	—	—
	n	23	17	21	17	22	19	22	19
LH	x	8.7	10.4	2.9	3.1	9.6	7.7	3.1	2.5
miu/l	s	5.1	6.2	1.3	1.8	5.0	3.9	1.6	0.8
	n	23	18	21	21	23	25	18	25
Log	x	2.29	2.38	2.53	2.55	2.32	2.31	2.72	2.73
Prolactin	s	0.22	0.26	0.18	0.20	0.20	0.19	0.21	0.21
miu/l	n	37	22	26	31	28	29	23	38
Log	x	0.14	0.39	0.70	0.69	0.25	0.20	0.69	0.69
Growth hormone	s	0.38	0.41	0.26	0.32	0.42	0.38	0.23	0.30
miu/l	n	35	20	25	31	26	29	23	38

Changes in plasma testosterone, oestradiol and LH on treatment occur predictably: therefore crude data given. Prolactin and growth hormone given after log transformation as skew distribution could influence more subtle changes on treatment.

per limit of the reference range. Mean oestradiol and testosterone concentrations were higher in patients without bone metastases (Table 1), but after log transformation to correct their distribution, differences between MO and MI patients were not significant. Conversely, mean plasma prolactin and growth hormone levels were higher in MI than MO patients but the difference was not significant after log transformation.

On Treatment

A few patients who developed metastases on treatment were regarded as MO before treatment and MI afterwards. However, their mean levels were no different from those of the main body of patients. There was no significant difference between MO and MI overall (Table 1) for any of the hormone measurements.

Testosterone

Plasma testosterone was invariably suppressed and to a similar extent by each of the drugs. A low initial plasma concentration below 8 nmol/l (8 patients) did not influence clinical response to treatment.

Oestradiol

Plasma oestradiol fell on treatment with DES. The difference between mean concentrations before and during treatment was highly significant (log mean +/−SD: 2.23 +/−0.24: 1.76 +/−0.17 respectively; T=3.98, $P = <0.001$). Conversely, on estramustine the levels invariably became highly elevated to values exceeding 4000 pmol/l.

Prolactin

(a) *Mean prolactin* increased significantly on both estramustine and DES (DES: T=2.04, $P = <0.05$; ES: T=4.06, $P = <0.001$). The mean concentration from patients on estramustine was significantly higher than for patients on DES (T=1.88, $P<0.05$).

(b) *Crossover studies*. The greater rise in mean prolactin on estramustine was supported by the results from patients crossed over from one drug to the other. The higher prolactin levels found in patients on estramustine were independent of whether the patients started with one or other drug (Fig. 1).

(c) *Effect on survival*. Four groups of patients were defined according to survival after start of treatment (0-1 year, 1-2 years, 2-3 years, 3 years+). Mean prolactin (after log transformation) tended to be lower as survival increased (0-1 year: 2.70 ± 0.25; 3 years+: 2.61 ± 0.21) but none of the differences was significant. The potentially unfavourable influence of an elevated plasma prolactin was also examined in a group of patients selected because they demonstrated very high levels (>1000iu/ml) at some time during their course. The group was small but it was clear that high levels were compatible with long survival and good response to treatment (Table 2).

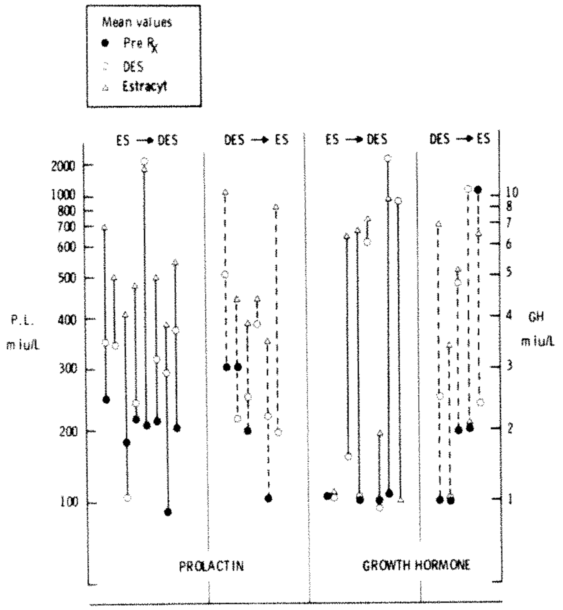

Fig. 1 Plasma prolactin (PL) and growth hormone (GH) in cross-over patients before treatment and serial mean concentrations on ES and DES.

Growth Hormone

A considerable rise in plasma growth hormone occurred on treatment (Fig. 1). There was no difference between mean values in patients on DES and those on estramustine (Table 1).

LH

A wide variation was seen in plasma LH levels before treatment. As for testosterone, LH was invariably suppressed by both forms of hormonal treatment (Table 1).

Effect of Inconsistent Compliance

In several patients known to be unreliable in their drug taking there was wide variation in the serial LH levels. In some cases the levels became elevated to well above pre-treatment values and corresponding to this there was an overshoot in the plasma tes-

Table 2 Survival in Response to Treatment in 14 Patients with Elevated Plasma Prolactin

Patient		*Range*	*Treat-ment*	*Survival (months)*	*Response to treatment*	*Bone metastases severity*
RW	38	230-1220	DES	A 65	1	
GS	74	650-1056	ES	A 51	1	
AS	96	440-3550	ES	D 31	1	
RH	100	792-1450	ES	A 35	1	
CH	17	840-2080	DES	D 17	1	
RH	14	1000-1582	DES	D 43	1	
FS	113	600-1015	ES	A 23	2	+
TR	98	940-3550 1902-2340	ES DES	A 44	2	+
JK	335	741-1012	DES	D 23	3	+ + +
RD	69	420-3161	ES	D 56	4	+ + +
HB	314	456-1020	ES	D 28	4	+ + + +
KC	48	420-1020	DES	D 12	4	+ + +
FH	14	840-1380	ES	D 13	4	+ +
SH	1	554-1060	DES	D 35	4	+ + +

D = dead. A = alive.

Response to treatment

1 = Stable. No bone metastases.

2 = Slow progression—development of new bone metastases.

3 = Good response of bone metastases.

4 = Rapid progression of bone metastases.

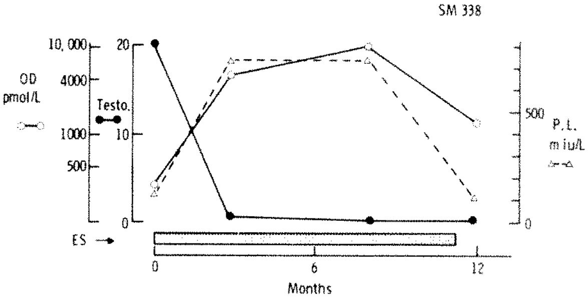

Fig. 3 Serial plasma oestradiol (OD), testosterone and prolactin in a patient on ES. Treatment was discontinued after 11 months.

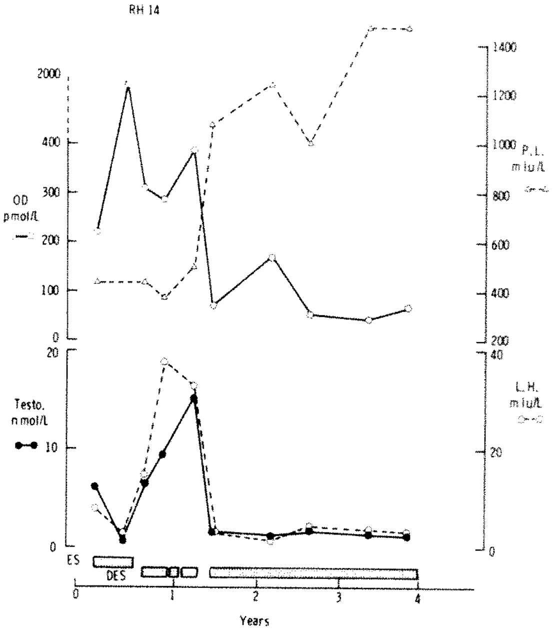

Fig. 4 Serial plasma oestradiol, testosterone, prolactin and LH in a patient on ES crossed over to DES.

tosterone (Fig. 2), although this rise was not invariable. Another effect seen in patients starting and stopping treatment was a corresponding rise and fall in prolactin (Fig. 3).

The extreme rise in oestradiol, a rise in prolactin and a fall in testosterone are shown in a patient treated with estramustine. Typically, prolactin fell rapidly and oestradiol to a lesser degree after treatment was discontinued (Fig. 3).

The hormone changes in a patient on both drugs are shown in Figure 4. Here treatment was begun with estramustine for a brief period, then followed with DES, taken inconsistently at first and afterwards regularly. In a second example, inconsistent administration of drugs was followed by wide swings in the plasma testosterone and a corresponding relapse in the biochemical markers of the disease (Fig. 5). In some patients, however, plasma testosterone remained suppressed, but a secondary rise in alkaline phosphatase occurred, reflecting intermittent failure of control of bone metastases because of missed treatment and corresponding to a rapid elevation of LH above pre-treatment levels. In other words, plasma LH was a better indicator of continued oestrogen administration in adequate dosage than testosterone. In 17 patients whose plasma LH was elevated at some time in the course

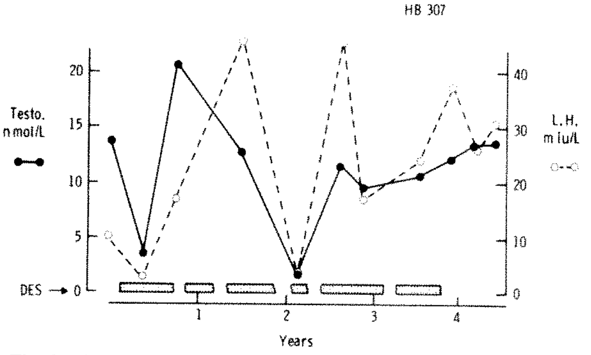

Fig. 2 Serial plasma testosterone and LH in a patient on DES. Treatment was frequently discontinued for short periods.

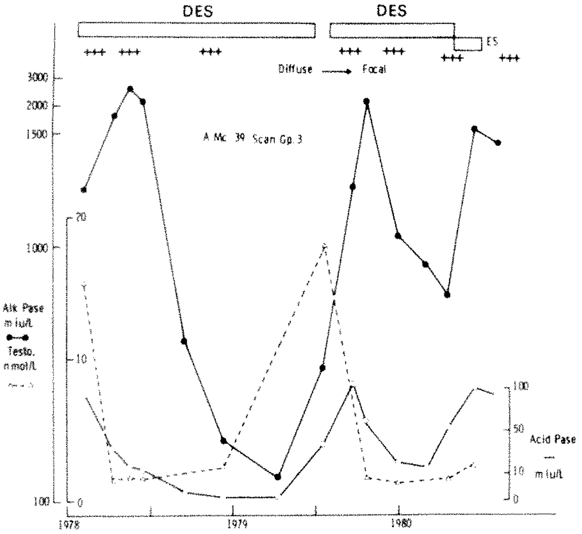

Fig. 5 Serial plasma testosterone, acid and alkaline phosphatase in a patient known to have temporarily discontinued treatment with DES. Treatment response groups as for Table 2.

of treatment, 7 maintained low plasma testosterone.

Discussion

The suppression of circulating testosterone by oestrogenic compounds, including DES and estramustine, is well documented elsewhere and confirmed here (Walsh, 1975; Karr *et al.*, 1980). Although oestrogens probably do have a direct effect upon prostatic and testicular androgen metabolism, the major inhibitory effect is upon gonadotrophin production by the anterior pituitary (Holland and Grayhack, 1976). In this respect, oestrogens and testosterone have a similar negative feedback action on the pituitary.

It is probably important to monitor plasma testosterone and check suppression of the pituitary-gonad axis (Robinson and Thomas, 1971; Shearer *et al.*, 1973; Walsh, 1975). In the present study an interesting byproduct of such routine measurements came from patients known to be inconsistent in their compliance. The considerable overshoot in LH after intermittent withdrawal of oestrogen suppression was unexpected and sometimes associated with a rise in plasma testosterone above normal. This may have potential importance if the aim is consistent suppression of androgen production and receptor function. In the present study, rapid relapse in the course of the disease was sometimes a consequence of intermittent hormone administration.

The phenomenon of LH overshoot could be useful in the context of a clinical trial for the prompt identification of the unreliable patient. The data reported here indicate that measurement of LH is probably more important than testosterone alone, since it seems to respond promptly and independently of plasma testosterone, whereas testicular interstitial cell function can remain permanently suppressed or recover only slightly. As oestrogens probably have a direct effect upon prostatic cancer, independent of androgen suppression, a patient whose disease has progressed clinically might not necessarily have become oestrogen-resistant but merely discontinued his therapy, despite low plasma testosterone levels. Examples of such patients were found in the present series and in these circumstances a rise in plasma LH was the key observation.

There is evidence that prolactin promotes the action of testosterone on the prostate (Harper and Griffiths, 1982). On the other hand, prolactin can have antigonadal activity: hyperprolactinaemia causes impotence and infertility perhaps through inhibition of the effect of the LH and FSH on the testes. Nevertheless, several workers have been convinced of the logic of combining prolactin suppression with oestrogens in the treatment of prostatic cancer (Jacobi *et al.*, 1980). Oestrogens are known to stimulate pituitary lactotrophs and elevate the serum prolactin in animals and normal women (Lloyd *et al.*, 1975). In the present study both forms of oestrogen led, as expected, to elevation of prolactin (Harper *et al.*, 1976). It is difficult to draw conclusions on any potential effect of prolactin on prognosis. In the present study, patients occasionally showed very high levels unrelated to stress or drug action other than oestrogen and their prognosis was not adversely affected. However, in the patients with bone metastases who were treated with estramustine, survival was significantly shorter than with DES (unpublished data). It is possible that the relatively high prolactin levels could have contributed, amongst other adverse factors. However, in practical terms, prostatic cancer responds and later relapses in a very predictable and qualitative fashion. Minor modifications of the suppression of hormone sensitive cells by oestrogens would be relevant only if the response was quantitative. At present there seems to be little justification in extrapolating directly from the laboratory studies and giving bromocriptine or other prolactin suppressing agents in addition to conventional hormone treatment.

The accentuated plasma prolactin rise on estramustine compared with DES may have been due to the larger effective dose of oestrogen in the compound estramustine. Certainly plasma oestradiol was very much elevated in patients treated in this group, whereas DES led to a slight fall in the level of oestrogen, confirming the results of other studies (Harper *et al.*, 1976; Jacobi, 1982). This disparity is not fully explained and it is not clear how much of the oestradiol is released during metabolism of the parent compound (Andersson *et al.*, 1981).

Others have suggested that patients with prostatic cancer might be distinguished from those with benign disease and patients with metastases at presentation separated from those without them on a basis of subtle differences in plasma hormone levels (Harper *et al.*, 1976; Bartsch *et al.*, 1977; British Prostate Group, 1979; Harper and Griffiths, 1982). We cannot comment on the first possibility as no control group was studied, although all mean hormone levels were within normal limits. The second proposition was examined simply. As in the study by the BPG/Tenovus Group, a trend towards slightly higher mean levels of growth hormone and prolactin in MI compared with MO groups was suggested. Conversely, plasma testosterone was higher in MO than MI. None of the differences was significant. These changes are of no more than casual interest.

It is concluded that routine follow-up laboratory assessment of patients with prostatic cancer should include testosterone and LH. Changes in prolactin probably warrant further research, but routine serial measurements are probably of little relevance in assessing the prognosis of individual patients.

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The Authors

M. C. Bishop, MD, MRCP, FRCS, Consultant Urologist, City Hospital, Nottingham.

C. Selby, MPhil, Principal Biochemist, City Hospital, Nottingham.

M. Taylor, FRCS, Consultant Urologist, Rotherham General Hospital, Rotherham.

Requests for reprints to: M. C. Bishop, Department of Urology, City Hospital, Hucknall Road, Nottingham NG5 1PB.

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Persistent Müllerian Duct Syndrome
Review and Report of 3 cases

S. J. SHEEHAN, I. N. TOBBIA, M. A. ISMAIL, D. G. KELLY and F. A. DUFF

Department of Urology, St Vincent's Hospital, Dublin, Eire

Summary—Three cases of persistent Müllerian duct syndrome are reported. All were phenotypically and karyotypically male but with persistent duct remnants. Problems encountered in management and surgery are discussed.

The persistence of Müllerian structures in the male is well recognised and more than 100 cases have been reported. Patients with this condition are phenotypically male with undescended testes. The syndrome was first described by Nilson in 1939 as hernia uteri inguinalis. The classical presentation is one of unilateral cryptorchidism with a contralateral hernia that contains Müllerian structures, including a fallopian tube or uterus. This variant is distinct from others in the dysgenetic male pseudohermaphrodite syndrome (Federman, 1968; Rabin and McKenna, 1982). Its recognition is of prognostic importance.

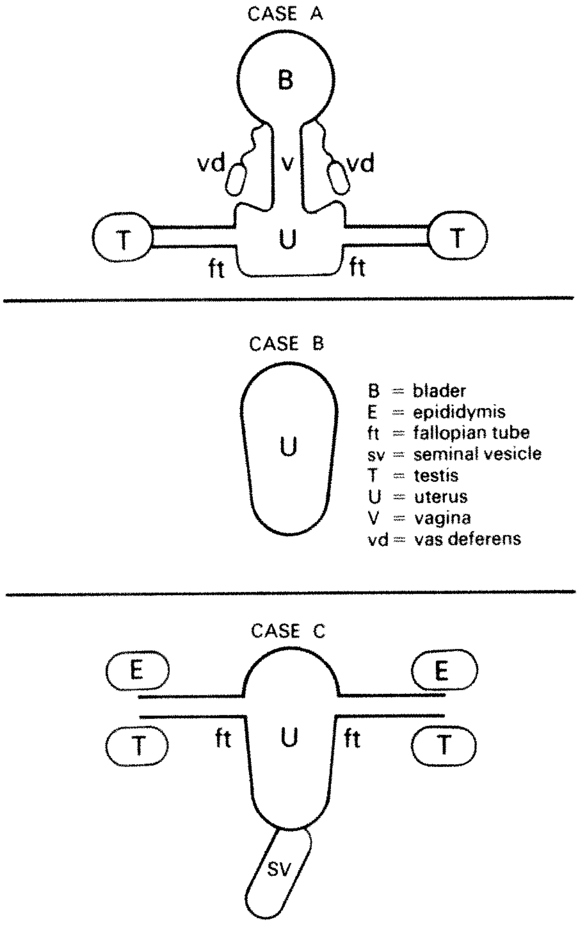

Fig. 1 Diagram of operative findings.

Patients

The details of three cases of persistent Müllerian duct syndrome are shown in Table 1. Two patients had bilateral cryptorchidism and the other an undescended left testis. Case A, a 9-month-old boy, had a small penis lying between pseudolabial folds. The other two had normal penile size and one, Case C, had normal male secondary sex characteristics and normal sexual function.

In no case were testes found in the superficial inguinal pouch or inguinal canal and laparotomy was performed. Case A was found to have hypoplastic testes attached to a uterus by two fallopian tubes (Fig. 1). The uterus, which contained urine, communicated with the posterior urethra through

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Table 1 Details of Patients

Patient	*Age*	*Presenting symptom*	*External genitalia*	*Internal genitalia*
A	9 months	Bilateral cryptorchidism	Bilateral cryptorchidism, small penis	Hypoplastic testes, uterus, 2 fallopian tubes, vagina
B	4 weeks	Left cryptorchidism	Left cryptorchidism, normal right testis, normal penis	Absent left testis, uterus
C	21 years	Bilateral cryptorchidism	Bilateral cryptorchidism, normal penis	Hypoplastic testes, uterus, 2 fallopian tubes, vagina

a vagina beside which were cord-like structures which were found to be vasa deferentia. No excision was performed at this time.

A urethrogram confirmed the operative findings of a communication between the uterus and urethra (Fig. 2). At laparotomy the uterus, vagina and fallopian tubes were excised and the testes placed deep to the internal inguinal ring.

Laparotomy in case B revealed a uterus which was excised, but neither vas nor testis were found on the left side. There were no fallopian tubes or vagina.

At exploration in Case C, testes were found. These could not be adequately mobilised and therefore orchiectomy was performed and prostheses inserted in the scrotum. A rudimentary uterus attached to a sac with no external orifice was noted. The sac was later found to be a seminal vesicle. Arising from the uterus were two fallopian tubes and two round ligament-like structures. An epididymis was located at the proximal end of each of these round ligaments. All of these structures were excised

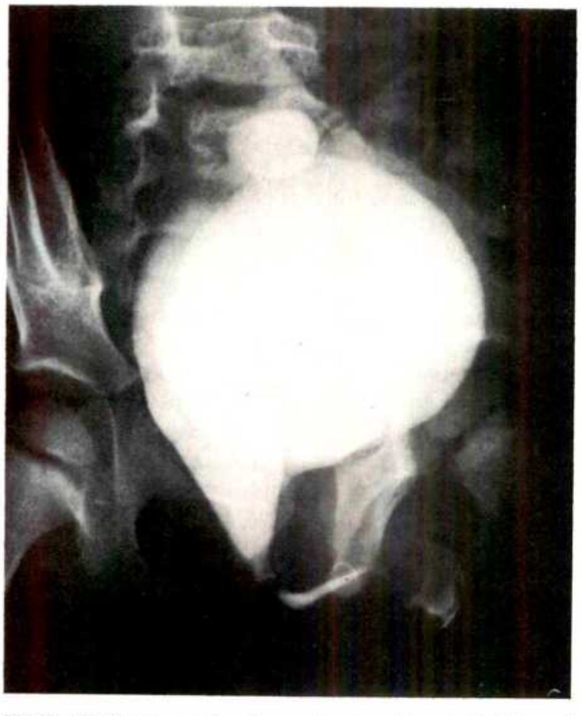

Fig. 2 Urethrogram showing contrast medium in bladder and vagina.

Subsequent investigations revealed that all three patients had a normal male karyotype (Table 2).

Table 2 Results of Investigations

Patient	*Karyotype*	*Testosterone, FSH, LH*	*Seminal analysis*
A	46 XY Chromatin negative	Normal	—
B	46 XY Chromatin negative	—	—
C	46 XY Chromatin negative	Normal	Absent spermatozoa

Two patients had normal testosterone, FSH and LH levels. Seminal analysis was possible in only one patient and showed absent spermatozoa.

These patients are undergoing endocrine evaluation. Only Case C is on testosterone supplements. Case A is to be reassessed in 2 years for consideration of a second stage orchiopexy.

Discussion

Female organogenesis follows a straight developmental line. Through the H-Y antigen on the Y chromosome, the development of a testis confers maleness on the indifferent tract by inhibiting the Müllerian ducts, stimulating the Wolffian ducts and masculinising the external genitalia. Development of the vasa deferentia, epididymis, seminal vesicles and external genitalia, together with regression of the lower vagina in the male fetus, is under the control of androgen secreted by the Leydig cells. Müllerian regression factor, secreted by the Sertoli cells, is responsible for retrogression of the Müllerian ducts. This hormone is secreted by the testis from the eighth fetal week up to 2 years of age and acts ipsilaterally (Donahoe *et al.*, 1977).

In pseudohermaphroditism the gonadal sex is at variance with the genital sex. The male pseudohermaphrodite has male gonads and karyotype but varying degrees of virilisation of the internal and external genital tracts. Many of these syndromes can be explained on the basis of defective formation or action of androgen or Müllerian regression factor.

Dysgenetic male pseudohermaphroditism is a group of disorders associated with testicular dysgenesis which are not due to defects in androgen biosynthesis or action. The development of the syndromes in this group is dependent on the stage of testicular differentiation at which the insult occurs (Rabin and McKenna, 1982). If gonadal failure occurs before organisation of the genital tract, female internal and external genitalia result, while gonadal failure occurring during the active period of male differentiation gives rise to imperfect sexual differentiation. There are five subgroups which span the clinical spectrum of dysgenetic male pseudohermaphroditism. At one end is XY gonadal dysgenesis or Swyer's syndrome, with failure of gonadal differentiation, female phenotype and reproductive tract and streak gonads. At the other end of the spectrum is congenital anorchia in which male differentiation is complete but testes are absent. There are three intermediate forms: rudimentary testis (Bergada's syndrome), hernia uteri inguinalis and mixed gonadal dysgenesis. In each of these syndromes there are varying degrees of testicular differentiation and also variable phenotype.

Cryptorchidism is not usually accompanied by the persistence of Müllerian duct derivatives. Several investigators have found that testes which fail to induce regression of the Müllerian system are often undescended. This gives rise to two possible explanations: firstly, that testicular descent is controlled by Müllerian regression factor and the lack of this hormone causes cryptorchidism (Donahoe *et al.*, 1977); secondly, that testicular descent is mechanically impeded by the inclusion of the gonad in the broad ligament and the decrease in Müllerian regression factor activity could be a consequence of this abnormal position (Josso *et al.*, 1983). The view that the syndrome is hereditary is supported by nine reported cases of familial occurrence. Autosomal recessive inheritance causing an inborn error of metabolism is one theory (Weiss *et al.*, 1978), while X-linked inheritance is suggested by the report of two affected brothers of different fathers (Brook *et al.*, 1973).

Several problems arise in association with the persistent Müllerian duct syndrome. Infertility is common, with absent spermatozoa on seminal analysis. However, there are six reported cases of fertility, although paternity was not established. Testicular malignancy appears to have an incidence similar to that of the "normal" cryptorchid child (Pappis *et al.*, 1979). Müllerian duct remnants may occasionally give rise to symptoms in the form of incontinence or retention cysts (Morgan *et al.*, 1979).

The three cases presented fulfil the criteria of persistent Müllerian duct syndrome in that they are phenotypically and karyotypically male but have persisting duct remnants.

The management of this condition is difficult because experience is limited. The diagnosis is seldom made pre-operatively but, if suspected, karyotyping is important, since the finding of an XY configuration may help the surgeon to decide between orchiopexy or orchiectomy. The incidence of testicular malignancy in mixed gonadal dysgenesis and Swyer's syndrome is 25 to 30%, while in the persistent Müllerian duct syndrome it is similar to that found in other cryptorchid children (Melman *et al.*, 1981; Rabin and McKenna, 1982).

All patients are phenotypically male and so the preservation of the external male appearance and maintenance of virilisation is essential. Primary or staged orchiopexy should accomplish this, though androgen supplements may be required.

The question of excision of the duct remnants remains unanswered. Excision of the vagina usually results in removal of the vas deferens as it is closely adherent to it. Since there may be unproven fertility in this syndrome, it may be advisable to leave the remnants *in situ* (Pappis *et al.*, 1979). There have been no reported cases of malignancy arising in persistent Müllerian ducts (Sloan and Walsh, 1976).

In suspected cases, laparoscopy is useful in planning the surgical management (Malone and Guiney, 1984). Finally, genetic counselling must be offered to the parents of these children because of the possible chromosomal origin of their syndrome.

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The Authors

S. J. Sheehan, FRCSI, Senior House Officer in Urology.
I. N. Tobbia, MB,BCh, MSc, Registrar in Pathology.
M. A. Ismail, MB,BCh, Registrar in Urology.
D. G. Kelly, MCh, FRCSI, Consultant Urologist.
F. A. Duff, MCh, FRCSI, Consultant Urologist.

Requests for reprints to: S. J. Sheehan, Cardiac Research Unit, Killingbeck Hospital, York Road, Leeds LS14 6UQ.

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Urethral Syndrome (Abacterial Cystitis)—Search for a Pathogen

J. TAIT, B. A. PEDDIE, R. R. BAILEY, E. P. ARNOLD, G. L. RUSSELL, V. A. BISHOP and A. F. BURRY

Departments of Nephrology, Urology and Pathology, Christchurch Hospital, Christchurch, New Zealand

Summary—Thirty-one women with the recurrent urethral syndrome (abacterial cystitis) had extensive microbiological, cytological and histological investigations. A *Streptococcus* species was isolated from the bladder aspirate of one patient, a wall-deficient *Streptococcus* species from two others and both a *Lactobacillus* species and *Ureaplasma urealyticum* from another. A possible microbiological cause was therefore identified in the bladder in only 4 of the 31 patients. A *Lactobacillus* species was isolated from the bladder aspirate of one control subject. Lactobacilli were grown in the voided urine of the majority of patients and in seven of the eight control subjects. *Chlamydia trachomatis* and *Herpes simplex* were isolated from the cervix and the urethra of one patient. Urethral cytology was normal in all patients. Trigonitis was noted at cystoscopy in 26 of the 31 patients. Bladder biopsies showed squamous metaplasia in 15 and lymphocytic infiltration of the lamina propria in 29, giving support to an inflammatory aetiology of this enigmatic syndrome.

Frequency of micturition, dysuria and other lower urinary tract symptoms are common in women. One-half of women with these symptoms will have a urinary tract infection (bacterial cystitis), while the remainder will have sterile bladder urine using conventional culture techniques and are regarded as having the urethral syndrome or abacterial cystitis (MRC Bacteriuria Committee, 1979). A number of explanations have been offered to account for this syndrome, including urethral and bladder neck obstruction, coital trauma, squamous metaplasia of the trigone, chemical irritation, stress, poor hygiene, nylon underwear and urinary tract infection with a number of unusual or fastidious infectious agents.

This study is a further attempt to isolate a possible infectious agent and to assess the cystoscopic and histological appearances of the trigone in women with this enigmatic syndrome.

Patients and Methods

Thirty-one patients who had been referred to this unit by their general practitioners because of recurrent lower urinary tract symptoms, but with sterile urine using conventional culture techniques, were studied. A questionnaire concerning details of symptoms, possible precipitating factors and past history was completed by each patient immediately before the investigations.

Urine specimens were cultured for a variety of micro-organisms and the results were compared with those obtained from eight control subjects. Specimens were also taken from the urethra, cervix and vagina for culture and cytological assessment.

The eight control subjects had no history of urinary tract symptoms, had taken no antimicrobial therapy during the past year and were undergoing elective minor gynaecological surgery (dilatation and curettage 4; laparoscopic tubal ligation 3; colposcopy and cone biopsy of cervix 1). All gave informed consent.

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Initial and midstream urine (MSU) specimens were obtained before general anaesthesia from 29 of the patients and from all of the control group. While under general anaesthesia a suprapubic bladder aspirate was obtained from all patients and controls. Swabs were taken from the urethra, vagina or cervix and from the anus. Cytological smears were taken from the urethra and the cervix and vagina. Cystoscopy was performed and endoscopic trigonal biopsies were taken from the patients, but not from the control subjects, for light and immunofluorescence microscopy.

Specimens obtained for cultures were transported immediately to the laboratory. All urine specimens and urethral swabs were inoculated to McConkey agar, blood agar, and chocolate agar plates, and incubated at 37°C aerobically and anaerobically in Gaspak jars. Bladder aspirate plates were incubated for up to 5 days if growth did not appear overnight. Specimens were inoculated on to Saboraud-Dextrose agar slants for fungal culture and Thayer-Martin plates with and without vancomycin-colistin-nystatin inhibitor for gonococcal culture. The Thayer-Martin plates were incubated for 48 h under reduced oxygen. Saboraud-Dextrose agar slants were incubated for 3 weeks. All urine specimens were also inoculated to thioglycollate broth, Robertson's cooked meat broth and the following enriched cooked meat media: Freake's meat, and Freake's broth supplemented with sucrose (10%) glucose (1%) and casein hydrolysate (1%). The thioglycollate broth and Freake's meat broth were for cultures of wall-deficient (L-phase) micro-organisms. Subcultures to blood agar from the broth media were made after 2 days and, if no growth was apparent, again at weekly intervals for 3 weeks. This was done to ensure that there were no fastidious organisms present in low numbers. Subcultures were incubated aerobically and anaerobically for 48 h. Cultures for *Ureaplasma urealyticum* and *Mycoplasma* species were done on filtered (22 and 45 μ, Gelman) urine specimens and urethral swabs from 24 of the patients and 2 of the controls. Mycoplasma broth and agar using mycoplasma agar base (BBL) and mycoplasma broth base (BBL), and T-strain broth and agar (mycoplasma base supplemented with urea) were used. The vaginal and anal swabs were cultured for gonococci and fungi.

Cervical and urethral swabs were cultured for *Herpes simplex* virus using HEp-2, Vero and HEL cell cultures, and for *Chlamydia trachomatis* in Hela 229 cell cultures, pre-treated with cycloheximide.

Results

The age range of the patients was 17 to 77 years (mean 36) and the control group 26 to 44 years (mean 32). Table 1 summarises information from the questionnaires. Frequency and urgency of micturition were the commonest symptoms and 27 patients had both of these symptoms, either alone or in addition to dysuria, nocturia, dyspareunia, suprapubic pain or perineal discomfort. The duration of urinary tract symptoms ranged from 3 months to 30 years with a mean of 6.8 years (SEM 1.2). The pattern of symptoms was the same in women over 35 years of age as in those under this age. Eleven of these 31 patients had undergone hysterectomy. Eight of 19 women who were premenopausal and had not had a hysterectomy considered that their symptoms were related to menstruation. Thirteen patients identified a possible factor precipitating each symptomatic episode (coitus 6, alcohol 2, emotional stress 2, miscellaneous 3). Seven patients and all of the control subjects admitted having had more than one recent sexual partner. A history of sexually transmitted disease was obtained from one patient and from none of the control group. Twenty-two patients had received at least one course of antimicrobial therapy for their symptoms despite negative urine cultures.

Table 1 Clinical Presentation of 31 Patients with Recurrent Abacterial Cystitis

Symptoms	*No. of patients*
Frequency	29
Urgency	27
Nocturia	21
Dyspareunia	19
Dysuria	14
Suprapubic discomfort	14
Perineal discomfort	11
Loin pain	10
Vaginal discharge	9
Haematuria	1

Bacteria were isolated from special cultures of the suprapubic aspirates from four patients and one control subject (Table 2). All four patients had recently received a course of antimicrobial therapy and conventional urine cultures had been sterile. A *Streptococcus* species was grown anaerobically from the direct culture on blood agar of one patient. Although the organism did not grow on the initial aerobic culture it grew both aerobically

Table 2 Microbiological Findings on Urine Specimens and Urethral Swabs

A. Patients *Organisms*	*Bladder aspirates (31)*	*MSUs (29)*	*Urethral swabs (31)*
Staphylococcus spp.	0	29	31
Streptococcus spp.	3	10 (4 aerobic, 6 anaerobic)	19 (13 aerobic, 3 anaerobic, 3 both)
Lactobacillus spp.	1*	24	29
Ureaplasma urealyticum	1*	4†	5‡
Escherichia coli	0	0	3
Proteus mirabilis	0	3	2
Other gram-negative bacilli	0	2	3
B. Control subjects *Organisms*	*Bladder aspirates (8)*	*MSUs (8)*	*Urethral swabs (8)*
Staphylococcus spp.	0	8	8
Streptococcus spp.	0	2	4
Lactobacillus spp.	1	7	8
Ureaplasma urealyticum	0	0†	0
Escherichia coli	0	3	2

* Denotes the same patient † Only cultured for in 24 patients and 2 controls

‡ Four of these 5 women had this organism in MSU and 1 in bladder aspirate

and anaerobically after subculture. Bladder aspirates of two other patients grew wall-deficient *Streptococcus* species (in Freake's broth plus sugar) which regained their cell wall when subcultured to blood agar. A *Lactobacillus* species and *Ureaplasma urealyticum* were grown from the bladder aspirate of one patient. The *Lactobacillus* species grew after incubation for 1 week in both Robertson's and Freake's broth. A *Lactobacillus* species was also grown from the bladder aspirate of one control subject after anaerobic incubation on blood agar.

The results of direct quantitative culture of MSU specimens are included in Table 3. The cultures of the initial urine specimens obtained from each patient grew the same organisms as in the MSU specimens and will not be considered further. Four patients had a bacterial count $>100\times10^6/1$ in their MSU specimen. Two of these were mixed morphological cultures of coagulase-negative *Staphylococcus* species and one had a pure growth of *Lactobacillus* species. None of these three patients had infected bladder urine. The fourth patient grew a mixed *Lactobacillus* species and coagulase-negative *Staphylococcus* species on anaerobic incubation, and a *Streptococcus* species grew on blood agar after anaerobic incubation. This was the patient who had a micro-aerophilic *Streptococcus* species in the bladder aspirate.

Streptococcus species did not grow from direct plating of the MSU specimens from the two patients who had cell wall-deficient *Streptococcus* species in the broth cultures of their bladder aspirates. Neither was the *Lactobacillus* species isolated from the MSU specimen of the patient whose bladder aspirate grew a *Lactobacillus* species after incubation in broth for 1 week, but a species of this organism was isolated, together with a coagulase-negative *Staphylococcus* species, from the MSU specimen of the control subject in whom a *Lactobacillus* species was grown from the bladder aspirate.

Lactobacillus species was found in MSU specimens from 10 patients and 4 control subjects after direct plating (Table 2). When broth cultures were incubated, this organism was found in 24 patients and 7 control subjects. Similarly, *Staphylococcus* species was isolated from MSU specimens of all patients and control subjects, but from only 22 patients and 6 control subjects on direct culture. *Ureaplasma urealyticum* was isolated from the voided urine of 4 of 24 patients but neither of the 2 control subjects. No *Mycoplasma* species was isolated.

Lactobacilli were cultured from the urethral swabs of 29 patients and all 8 controls. *Neisseria gonorrhoea* was not grown from the urethral, vaginal, cervical or anal swabs of any patient or control subject. *Chlamydia trachomatis* and *Herpes simplex* were both isolated from the cervical and urethral swabs of the woman with an anaerobic *Streptococcus* in her suprapubic aspirate. A yeast was cul-

Table 3 Quantitative Counts from Direct Cultures of MSU Specimens

Bacterial count	*Patients (29)*	*Control (8)*
$>100 \times 10^6$/l	4 *Staph spp.* 2 *Lactobacillus spp.* 1 *Lactobacillus spp.* + *Staph spp.* + *Strep spp*† 1	0
20-50 $\times 10^6$/l	6 *Staph spp* 3 *Staph spp* + *Lactobacillus spp* 2 *Staph spp.* + *E coli* (7 colonies) 1	2 *Staph spp* + *Lactobacillus spp.* 1*† *Staph spp.* + *Lactobacillus spp.** + *Strep spp.* 1
$<20 \times 10^6$/l	14 *Staph spp.* 6 *Lactobacillus spp.* 1 *Staph spp.* + *Lactobacillus spp.* 3 (1*) *Staph spp.* + *Pr mirabilis* (5 colonies) 1 *Staph spp.* + *E. coli* (4 colonies) 1 *Staph spp.* + *Strep spp.* + *Lactobacillus spp.* 2*	5 *Staph spp.* 2 *Lactobacillus spp.* + *E. coli* (6 colonies) 1 *Staph spp.* + *E. coli* (1 colony) 1 *Staph spp.* + *E. coli* (2 colonies) + *Lactobacillus spp.* 1*
Sterile	5	1

* *Lactobacillus* initially grew in anaerobic culture only   † Infected bladder aspirate

tured from three symptomatic patients and one control subject. In all cases it was isolated from the vagina, but from two of these patients it was also found in the urethral culture. Three other women had a yeast cultured from their anal swabs.

Atypical cytology was found in the cervical smears of five patients (inflammatory effect in 4, mild dysplasia in 1) but in none of the controls. Urethral cytology was normal in all patients.

Trigonitis was diagnosed endoscopically in 26 of the 31 women, including all 4 with an isolated bladder organism. Five of these 26 women also had inflammation of the adjacent bladder mucosa. The epithelium was histologically abnormal in 21 of the total, showing squamous metaplasia in 15 and being hyperplastic in six. Of the 15 women with squamous metaplasia, five had undergone hysterectomy and only two were post-menopausal. In 15 of the 31 patients there was histological evidence of fibrosis. Lymphocytic infiltration of the lamina propria was seen in the biopsies of 29 women and was present even when the trigone appeared endoscopically normal. The severity of the lymphocytic infiltration did not correlate with the severity of the appearances at cystoscopy, nor with the length of the patient's history. Suitable histological material was available for fluorescence microscopy on 21 patients. IgA deposits were detected within the cytoplasm of some epithelial cells in one patient and in the lymphoid cells of another. The remainder showed no abnormal plasma protein deposition.

Discussion

Is an infectious agent responsible?

In this study we attempted to culture a wide range of infectious agents from women presenting with the urethral syndrome. In only 4 of 31 patients was a possible pathogen isolated from the bladder aspirate. In two of these women, cell wall-deficient *Streptococcus* species was cultured using special media. These are organisms that have been exposed to antibiotics that destroy the cell wall (*e.g.* penicillins, cephalosporins) and later revert to their original type. This was demonstrated by subculturing them to blood agar.

By using special culture techniques, organisms found in both initial and MSU samples reflected the commensal urethral flora; this applied to both our patients and control subjects.

In the latter group, despite no past history of urinary infection or other urinary symptoms, three grew a few colonies of *Escherichia coli* (1, 2 and 6×10^6/l) from the MSU, although none had the organism cultured from the bladder aspirate. This is not altogether surprising, since enterobacteria have been isolated from the urethra of 10 to 58% of healthy women (Bailey *et al.*, 1973).

Most women do not have urinary symptoms despite harbouring a resident urethral flora similar to that of those who do get urinary symptoms. The role of organisms cultured from urethral swabs and voided urine samples, in the aetiology of the urethral syndrome, remains unclear.

Maskell *et al.* (1979) were able to isolate fastidious slow-growing organisms, particularly *Lactobacillus* and *Corynbacterium* species, from all MSU samples of a group of 73 women diagnosed as having the urethral syndrome, and postulated that these bacteria were responsible for the symptoms. Bacterial counts between 10 and 100×10^6/l on MSU specimens were regarded as positive. More recently this group of workers (Maskell *et al.*, 1983) have confirmed their earlier findings and demonstrated a highly significant relationship between counts of fastidious organisms in voided urine and the presence of symptoms.

On the other hand, Brumfitt *et al.* (1981) reported no significant difference between the isolation rate of lactobacilli in urine cultures from healthy women and women with the urethral syndrome. This conclusion needs to be reserved as some of their controls had previously experienced up to two episodes of urinary tract symptoms, unlike our control subjects. However, our findings would support their view, despite the fact that we studied only eight controls.

Stamm *et al.* (1980) have suggested that the urethral syndrome may be caused by conventional pathogens (*e.g.* coliforms, *Staphylococcus saprophyticus*) in low numbers, or by *Chlamydia trachomatis*. We consider, however, that patients with low bacterial counts of conventional pathogens simply have bacterial cystitis. Of 32 women with sterile bladder urine, 10 of 16 with pyuria and 1 of 16 without pyuria were infected with *Chlamydia trachomatis* (Stamm *et al.*, 1980). We and others (Burney *et al.*, 1983) have not found this organism to be as troublesome as Stamm *et al.* (1980). Neither have we isolated *Ureaplasma urealyticum* as commonly as McDonald *et al.* (1982).

Is there evidence of an inflammatory process?

The symptoms of dysuria, urgency, urethral pain and dyspareunia might suggest an inflammatory cause. Tenderness and thickening of the urethra and trigone on vaginal palpation are not invariably present but, when present, are difficult to quantify. The same applies to the endoscopic appearances in the urethral syndrome, including varying degrees of granular and membranous trigonitis and occasionally congestive changes in the proximal urethra. However, the same trigonal appearances are sometimes seen when cystoscopy is performed on women without the urethral syndrome.

In our study the presence of an abnormal lymphocytic infiltration in the trigonal biopsies of 29 of 31 patients, and fibrosis in 15, suggested a chronic inflammatory response associated with the urethral syndrome. Occasional lymphocytes are demonstrated in the lamina propria of the normal bladder, but an increase in the number of lymphocytes is quite non-specific and characteristic of an inflammatory process from any cause. The possibility of an immunological cause was not supported by our findings and the pathological changes gave no clue to the aetiology of the condition.

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The Authors

J. Tait, MB,BS, MRCOG, Urology Registrar.
B. A. Peddie, PhD, Research Bacteriologist.
R. R. Bailey, MD, FRACP, FRCP, Head of the Department of Nephrology.
E. P. Arnold, PhD, FRCS, FRACS, Associate Professor of Urology.
G. L. Russell, MB,ChB, Urology Registrar.
V. A. Bishop, RN, Nurse-Technician.
A. F. Burry, MD, ChB, FRCPA, Pathologist.

Requests for reprints to: R. R. Bailey, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.

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A Comparative Study of Various Electrodes in Electromyography of the Striated Urethral and Anal Sphincter in Children

K. K. NIELSEN, E. S. KRISTENSEN, N. QVIST, K. M.-E. JENSEN, J. DALSGÅRD, T. KRARUP and D. PEDERSEN

Departments of Urology and Paediatrics, Aalborg Hospital, Aalborg, Denmark

Summary—The series comprised 41 children aged 6 to 14 years consecutively referred with recurrent urinary tract infection and/or enuresis. Carbon dioxide cystometry was carried out in the supine and the erect position and combined with simultaneous electromyography (EMG). The external urethral sphincter was examined with a ring electrode mounted on a urethral catheter, while recordings from the striated anal sphincter were based on an anal plug electrode and perianal electrocardiographic (ECG) skin electrodes: 211 EMG and cystometric examinations were performed and all three methods gave satisfactory results. Correlation between them was good, as was reproducibility. Perianal surface ECG electrodes are recommended for the evaluation of functional disturbances of the external sphincter. They are painless, easy to use, and are well tolerated by the patient.

Voiding abnormalities are often encountered in paediatric practice. In the evaluation of these problems EMG recording from the external urethral or anal sphincter, combined with cystometry, urethral pressure profile measurement or pressure-flow studies, has gained widespread recognition (Blaivas *et al.*, 1977; Firlit *et al.*, 1978). EMG recording from the external urethral sphincter may be obtained by the percutaneous insertion of needle electrodes or by a ring electrode mounted on a urethral catheter (Bradley *et al.*, 1974; Nordling *et al.*, 1978). Recordings are usually obtained from the external anal sphincter because its activity also reflects the function of the external urethral sphincter (Maizels and Firlit, 1979). Examination of the external anal sphincter is performed either with needle electrodes inserted percutaneously or surface electrodes in the shape of the anal plug or ECG plaster electrodes (Barrett, 1980). Because of problems in applying the electrodes and consequent lack of patient co-operation, the use of bipolar anal surface electrodes has become increasingly popular (Maizels and Firlit, 1979; Barrett, 1980).

In choosing electrodes for electromyography several factors have to be considered: (1) the quality of the recording, including reproducibility, (2) agreement between external anal and urethral recordings, and (3) patient co-operation. The purpose of the present study was to evaluate these factors in three types of electrode: the urethral ring electrode, the anal plug, and the perianal ECG surface electrode.

Patients and Methods

The series comprised 41 neurologically normal children referred consecutively with recurrent urinary tract infection with or without incontinence (36 children) or primary enuresis (5 children) between November 1981 and March 1983. The median age was 9 years (range 6-14). Only three patients (7%) were male. All patients underwent detailed investigations including history, physical examination, routine blood chemistry, spontaneous uroflowmetry, ultrasound residual urine determination, urine culture, intravenous urography and voiding cystography. All children had negative urine cultures.

During admission carbon dioxide cystometry using a transurethral 10 F catheter was performed

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with a filling speed of 100 to 200 ml/min (DISA cystometer type 21G01). Simultaneous EMG recordings were taken from either the external urethral sphincter, using a bipolar ring electrode mounted on the catheter tip (Nordling *et al.*, 1978), or from the striated anal sphincter using a bipolar-anal plug or two ECG electrodes situated perianally at 2 and 10 o'clock respectively (DISA EMG amplifier type 21C01). The test was carried out with the patient in the supine and the erect position for each of the three methods, *i.e.* 6 times per patient. Detrusor instability (DI) was defined as uninhibited detrusor contractions exceeding 15 cm H_2O in at least two of the tests.

Cystourethroscopy, with insertion of a suprapubic catheter for pressure-flow and EMG studies, was performed under general anaesthesia. Two hundred and eleven cystometry/EMG recordings were carried out. Thirty-two children underwent all 6 tests. Two patients were not examined because of lack of co-operation. One patient had no EMG recording and two had only cystometry and urethral EMG owing to painful DI. Two patients refused to have the anal plug inserted and in two cases the ring electrode was wrongly located.

Evaluation of the quality of the EMG recordings obtained with each type of electrode was based on the amplitude of the signal using a fixed amplification factor and on the reproducibility of the EMG response in two tests. The amplitude of the signal during sphincter contraction was regarded as satisfactory if it was twice as high as in the relaxed state. The test result was regarded as reproducible if the signal was identical in two recordings from the same electrode.

Detrusor external sphincter dyssynergia was defined as unchanged or increased EMG activity during voluntary detrusor contraction, while synergia was defined as decreased EMG activity during contraction. During uninhibited detrusor contractions a marked increase in EMG activity is usually observed (Mayo, 1979) and this is known as voluntary detrusor sphincter dyssynergia. The outcome of cystometry was classified as either abnormal (*i.e.* DI) or normal.

Results

Cystometry was found to be normal in 22 children and 17 had DI. With regard to EMG amplitude, a high proportion of satisfactory recordings resulted from all types of electrode (Table 1). Reproducibility was 100% for the ring electrode (95% confidence limits 88-100%), 88% for the perianal ECG skin electrodes (95% confidence limits 71-96%) and 87% for the anal plug (95% confidence limits 70-96%). A high degree of correlation was demonstrated between the various types of EMG recordings (Table 2). The correlation between the urethral ring electrode and the perianal ECG skin electrode was 88% (95% confidence limits (68-96%), between the perianal ECG electrodes and anal plug it was 90% (95% confidence limits 74-97%), and 86% (95% confidence limits 68-96%) between the ring electrode and the anal plug.

Table 1 Recording of EMG Amplitude

Electrode	*Satisfactory number (%)*	*Unsatisfactory number (%)*
Urethral ring	65 (92)	6 (8)
Anal plug	62 (91)	6 (9)
Anal surface	67 (93)	5 (7)

Table 2 Agreement between the Different Types of EMG Recordings in 22 Children with Normal and 17 with Abnormal Cystometry

Cystometry	*Ring electrode/ anal surface*	*Ring electrode/ anal plug*	*Anal surface/ anal plug*
Normal cystometry			
synergia	15	15	15
Agreement			
dyssynergia	1	1	3
Disagreement	3	3	2
Total	19	19	20
Abnormal cystometry			
synergia	9	8	7
Agreement			
dyssynergia	3	1	3
Disagreement	1	1	1
Total	13	10	11

Some patients have been omitted because of technical difficulties during recording.

Discussion

Electromyography from the external urethral sphincter and anal sphincter has proved valuable in the evaluation of the lower urinary tract. Generally it concerns demonstration of the presence of absence of EMG activity in the external urethral sphincter during the bulbocavernosus reflex and in uninhibited or voluntary detrusor contractions. Mayo (1979) recommended that sphincter activity should be recorded with a special electromyographic detector and oscilloscope, while others claimed that most voiding disorders are adequately tested by integral EMG, as in the present study (Bradley *et al.*, 1974; Barrett, 1980).

We found that all of the electrodes tested produced recordings suitable for clinical practice. Our results with the anal plug were better than those reported by other workers. This might be due to the use of different criteria in judging what constitutes a satisfactory amplitude. Results with the urethral ring electrode and the perianal ECG electrode were similar to those of other workers (Maizels and Firlit, 1979; Barrett, 1980; King and Teaque, 1980). Reproducibility of EMG recordings made with the ring electrode was high, as was shown also by Maizels and Firlit (1979). Some authors have claimed that EMG activity increased because of gas leakage around the catheter during detrusor contraction, causing insufficient contact between the electrode and the urethral mucosa. However, this artefact occurred only in patients previously subjected to urethral surgery, *e.g.* prostatectomy and sphincterotomy (King and Teaque, 1980). Reproducibility with perianal ECG electrodes was slightly worse than with the ring electrode, a finding also reported by Maizels and Firlit (1979). This might be because the skin electrodes, as a result of their size, record from a larger area and thus do not reflect the activity in a single well defined group of muscles. We found that recordings from the anal plug were more reliable than those described by other workers (Maizels and Firlit, 1979; King and Teaque, 1980).

It remains unclear whether both the external urethral and anal sphincter are innervated by the pudendal nerve. Some authors support this point of view (Tanagho *et al.*, 1982), while others claim that the fast-twitch fibres of the extrinsic component of the external sphincter are supplied by the pudendal nerve and the intrinsic component, which are slow-twitch fibres, have splanchnic innervation (Donker *et al.*, 1976; Gosling and Dixon, 1979).

Studies of neurogenic bladder dysfunction have revealed a considerable degree of dissociation in the EMG activity of the external urethral and anal sphincter (Nordling and Meyhoff, 1979), while in neurologically normal persons a significant number of identical recordings have been obtained (Maizels and Firlit, 1979).

With regard to patient compliance, the perianal ECG electrodes were superior to the other types. They are painless and easy to apply. They also allow the patient to be fully mobile and thus ensure that the test can be easily performed in various positions. The disadvantage is that they record from a large area and not necessarily from the sphincter alone. The anal plug is not well tolerated, while the ring electrode is a good method for patients who for other reasons are catheterised transurethrally, *e.g.* cystometry. The ring electrode, however, may be difficult to place correctly, resulting in repeated catheterisations.

It is concluded that perianal ECG skin electrodes are a simple and reliable means of obtaining EMG recordings in patients with voiding disorders.

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The Authors

K. K. Nielsen, MD, Urological Registrar.
E. S. Kristensen, MD, Urological Registrar.
N. Qvist, MD, Urological Registrar.
K. M.-E. Jensen, MD, Urological Registrar.
J. Dalsgård, MD, Urological Registrar.
T. Krarup, MD, PhD, Chief Urologist.
D. Pedersen, MD, Paediatric Registrar.

Requests for reprints to: K. K. Nielsen, Kommenhaven 27, st. th., 2730 Herlev, Denmark.

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The Management of Early Stage Non-seminomatous Germ Cell Tumours of the Testis: Edinburgh 1970-1981

W. DUNCAN and A. J. MUNRO

Department of Clinical Oncology, Western General Hospital and Royal Infirmary, Edinburgh

Summary—This study describes the management of early stage non-seminomatous germ cell tumours of the testis in Edinburgh between 1970 and 1981.

There were 69 patients in clinical Stage I and 22 patients in clinical Stage IIA. All were treated by orchiectomy and radiotherapy to the para-aortic nodes. Some of the patients with Stage IIA disease received additional therapy.

The overall 5-year actuarial survival rate was 83%. In a group of 52 patients with Stage I disease who had had lymphography as part of their initial staging the 5-year actuarial survival rate was 94.2%.

The overall relapse rate was 27/91 (29.7%). The relapse rate in State IIA disease was 11/22 (50%) and the 5-year actuarial survival rate was 64%. Patients with primary tumours beyond T1 had a significantly higher relapse rate than patients with T1 primary tumours: 10/20 (50%) and 13/52 (25%) respectively. The histology of the primary tumour did not have a statistically significant influence upon relapse rate.

There is currently considerable uncertainty concerning the role of radiotherapy in the management of early stage non-seminomatous germ cell tumours of the testis (NSGCTT).

Recent advances in diagnostic techniques and the availability of effective chemotherapy for metastatic testicular cancer have led some centres to abandon prophylactic retroperitoneal irradiation for early stage NSGCTT (Peckham *et al.*, 1982; Oliver *et al.*, 1983; Peckham *et al.*, 1983; Read *et al.*, 1983).

There are surprisingly few recent data on the results of prophylactic radiotherapy in properly staged patients with NSGCTT who have no clinical evidence of metastatic disease. This paucity of information has prompted the current review.

Patients and Methods

The clinical records of all patients treated for malignant testicular neoplasms at the Department of Radiation Oncology, Western General Hospital and Royal Infirmary, Edinburgh, during the period 1970 to 1981 (inclusive) have been reviewed. The total number of patients for review was 336.

Seventeen patients (5%) did not have germ cell tumours. Of the 319 patients with germ cell tumours, 187 (58.6%) had seminomas and 132 (41.4%) had non-seminomatous or mixed histology tumours. The 132 patients in this latter group were clinically staged according to the Royal Marsden Hospital stage grouping (Peckham *et al.*, 1981), but without being subjected to their routine staging procedures.

Staging policies for testicular cancer changed during the period under consideration. Patients who presented before 1973 were staged on the basis of history, physical examination and chest X-ray, with or without intravenous urography (IVU). All patients presenting subsequently also underwent bipedal lymphography (LAG). Analysis of serum tumour markers (α fetoprotein; β subunit of human chorionic gonadotrophin) was performed only after 1977. Computed axial tomography (CT)

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became available in 1981. Only six patients had CT scanning as part of their initial staging.

There were 69 patients in clinical Stage I (disease apparently confined to the testicle) and 22 in clinical stage IIA (para-aortic nodal metastases present but no lesion greater than 2 cm in diameter). These 91 patients formed the basis of the present review.

No patient was lost to follow-up and all were followed up for a minimum of 2 years since their first treatment (mean 5.34 years; median 5 years; maximum 11 years).

The histology of the primary tumour was classified according to the UK Testicular Tumour Panel classification (Pugh and Cameron, 1976). Where possible, TNM T-staging was also applied (UICC, 1978).

All patients with Stage I NSGCTT were treated with a standard radiotherapeutic technique. Parallel opposed fields, encompassing a volume best described as a truncated pyramid, were used. The field extended from the upper border of T11 to the root of the penis. The fields thus included the para-aortic and iliac nodes bilaterally. The kidneys were excluded from the fields of irradiation. The dose given was 3500 cGy in 20 daily fractions in 4 weeks (prescribed at midplane) using a 6 MV or 9 MV linear accelerator. Both fields were treated daily.

Patients with Stage IIa disease were managed by a variety of different policies during the period of this study. All received sub-diaphragmatic irradiation as described above. Ten patients received no further elective treatment. Eight received prophylactic irradiation to the mediastinum and left supraclavicular fossa and four were treated with adjuvant chemotherapy (vinblastine and bleomycin).

Actuarial analysis of survival and relapse-free survival was performed using life tables (Mould, 1976). Since all of the deaths were attributable to testicular cancer, no age correction was applied. Statistical significance was assessed using chi-squared testing.

Results

The histological classification of the primary tumours in the 91 patients is shown in Table 1. For the purposes of subsequent discussion the mixed tumours were included within the appropriate non-seminomatous category. There was sufficient information to permit T-staging in 72 patients. The primary tumour was classed as T1 in 52 patients; 20 had primary tumours beyond T1.

Table 1 Histological Classification of Primary Tumours in the 91 Patients

Histology	*No. of patients*
Malignant teratoma undifferentiated (MTU)	36 (40%)
Malignant teratoma intermediate (MTI)	34 (37%)
Mixed tumours	18 (20%)
MTU + seminoma	8
MTI + seminoma	8
TD + seminoma	2
αFP producing "Seminoma"	1
Teratoma differentiated (TD)	2

αFP = alphafetoprotein

The 5-year actuarial survival data are presented in Table 2. The actuarial relapse-free survival curve for all 91 patients is shown in Figure 1.

Relapse occurred in 27/91 patients (29.7%). Figure 2 shows the cumulative time to relapse curve for these patients. The range of times to relapse was 0.1 to 4.0 years (mean 0.55 years; median 0.25 years). A detailed analysis of relapse sites is presented in Table 3.

Ten of the 27 patients with recurrent disease were treated successfully. Seventeen died from uncontrolled testicular cancer. Of the 13 patients who relapsed before 1978, only three were successfully treated. This reflects the inadequacy of the chemotherapy available at that time. Fourteen patients relapsed after 1978 and seven of these have survived (without further evidence of disease) for at least 2 years after their last treatment.

The results of treating recurrent disease in the 11 Stage I patients who relapsed, and who had had lymphography as part of their initial assessment, were as follows. Five were successfully treated with further radiotherapy. One patient, with a scrotal recurrence, was cured by surgery. Two patients were cured with chemotherapy. Only 3 of the 11 patients died from testicular cancer—they failed to

Table 2 Actuarial Survival Data

Group	*No. of patients*	*Five-year actuarial survival*
I + IIA	91	83.0%
I with lymphogram	52	94.2%
IIA	22	64.0%
I + IIA (T1)	52	88.0%
I + IIA (T>1)	20	74.2%

Table 3 Analysis of Relapses by Site and by Initial Clinical Stage

			Relapse sites						
Clinical stage	*No of patients at risk*	*No. of relapses*	*Lung*	*PA*	*Nodes MED*	*SCF*	*Brain*	*Other bone*	*Scrotum*
I (No lymphogram)	16	5	4	—	1	—	—	1	—
I (lymphogram)	52	11	5	1	2	4	—	—	2
IIA	22	11	8	2	—	3	2	—	—

PA = para-aortic MED = mediastinal SCF = supraclavicular fossa

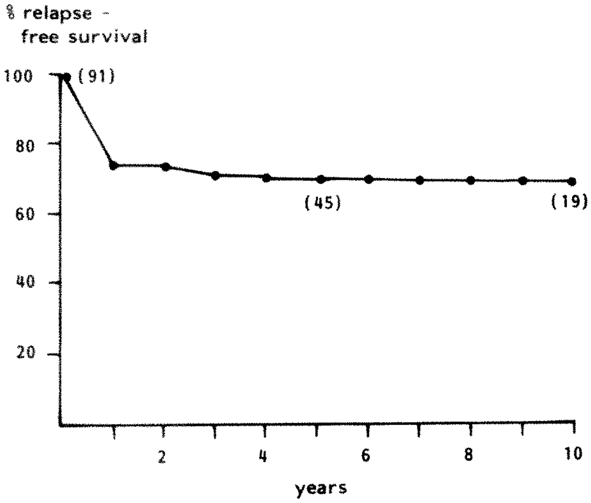

Fig. 1 Actuarial relapse-free survival for the 91 patients. Figures in brackets indicate number of patients at risk at the specified time.

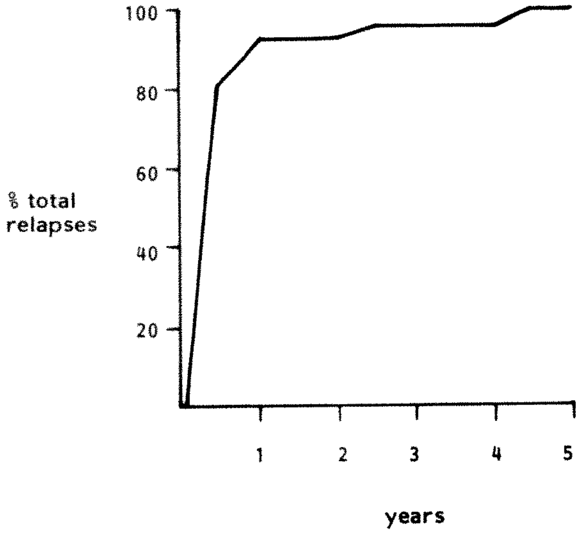

Fig. 2 Cumulative time to relapse curve for the 27 patients whose disease relapsed after initial therapy.

respond to chemotherapy, with or without additional radiotherapy.

The relapse rates (by histology, and including patients with tumours of mixed histology within the appropriate non-seminomatous category) were: malignant teratoma undifferentiated (MTU) 17/44 (38.6%); malignant teratoma intermediate (MTI) 10/42 (23.8%). This difference was not statistically significant ($P > 0.1$).

For patients with T1 primary tumours the relapse rate was 13/52 (25%), whilst for primary tumours greater than T1 the relapse rate was 10/20 (50%). This difference was statistically significant ($P < 0.05$: >0.025). Relapse rates, according to histology and T stage in the 52 patients who had Stage I disease and who had had lymphography, are shown in Table 4.

There were 22 patients in this series with Stage IIA disease. Radiotherapy failed to control the retroperitoneal disease in 2/22 patients. A further nine patients developed recurrent disease elsewhere. Thus the overall relapse rate in Stage IIA was 11/22 (50%). This compared with 11/52 (21.2%) for patients with Stage I disease, based on negative lymphography. This difference was statistically significant ($P < 0.025$; >0.01).

The morbidity associated with retroperitoneal irradiation was minimal. All patients experienced

Table 4 Relapse Rates by Histology and T Stage for 52 Patients with Stage I Disease whose Initial Evaluation had Included Lymphography

	MTU	*MTI*	*TD*	*All*
Tx	1/5	0/5	—	1/10
T1	3/15	3/13	0/3	6/31
T>1	3/6	1/5	—	4/11
All	7/26	4/23	0/3	11/52

MTU = malignant teratoma undifferentiated
MTI = malignant teratoma intermediate
TD = teratoma differentiated

some malaise and nausea. Any vomiting or diarrhoea usually responded well to symptomatic treatment. No patient required hospital admission for acute side effects related to radiation therapy.

Most patients developed transient myelosuppression during radiotherapy but all were able to complete their scheduled sub-diaphragmatic irradiation.

Two of eight patients, who were supposed to receive prophylactic radiotherapy to the mediastinum and left supraclavicular fossa, had their supradiaphragmatic irradiation abandoned because of leucopenia.

One patient developed acquired lactose intolerance; otherwise there was no detectable long-term morbidity from treatment.

No patient has developed a second malignancy. There has been no routine assessment of fertility after treatment.

Discussion

The Department of Radiation Oncology, Western General Hospital and Royal Infirmary, Edinburgh, is a regional centre serving a geographically defined population. The experience of such a department should, therefore, reflect the true incidence of malignant disease within the community it serves. The incidence of testicular cancer in Scotland is currently 3.2 new patients per 100,000 men per year. The Edinburgh department serves a total population of 1.75 million (of whom 875,000 are men). The expected number of new patients with testicular cancer within this defined population during the 12 years of the study period can therefore be calculated as 336. This agrees precisely with the observed number of referrals.

The observed proportions of non-germ cell tumours, seminomas, tumours of mixed histology and non-seminomatous germ cell tumours are in agreement with most other population-based series (Pugh and Cameron, 1976). We can, therefore, be fairly certain that the current review accurately reflects a community experience.

The actuarial relapse-free survival curve for the 91 patients shows an initial steep decline followed by a long plateau (Fig. 1). The 5-year and 10-year actuarial relapse-free survival figures are identical (70.9%). This indicates that patients who have survived 5 years after treatment are likely to be cured. When relapse occurs it usually occurs soon (less than 18 months) after treatment. Late relapses are uncommon (Fig. 2).

In this review, overall survival is a less consistent measure of the effectiveness of initial therapy than is relapse-free survival. This is because effective chemotherapy was not used in Edinburgh until 1978, when the first patients were treated with cisplatin, vinblastine and bleomycin (Einhorn and Williams, 1980). Patients who relapsed after 1978 therefore had a better chance of long-term survival than those who relapsed before 1978.

Although the histology of the primary tumour appeared to influence the relapse rate, with MTU tumours more likely to relapse than MTI tumours, this difference was not statistically significant. This could be the result of a Type II statistical error, in that the population under investigation was too small for conventional statistical significance to be achieved.

Surveillance studies have produced conflicting data concerning the influence of histology upon relapse rate. The study from the Royal Marsden Hospital, London, by Peckham *et al.* (1983) showed a higher relapse rate in patients with MTU tumours (40.7%) than in patients with MTI tumours (6.8%). The study from the Christie Hospital, Manchester, showed no predominance of MTU tumours amongst patients who relapsed (Read *et al.*, 1983). The DATECA study (Schultz *et al.*, 1984) was unable to demonstrate any influence of histology upon relapse rate. The data from Milan (Pizzocaro *et al.*, 1984) suggested that the presence of "teratomatous elements" was associated with a lower relapse rate.

In the present study, tumours confined to the body of the testis (T1) were associated with a lower relapse rate than tumours which had breached the tunica albuginea or involved adjacent structures ($T > 1$). These results confirmed those of others (Sandeman and Matthews, 1979; Batata *et al.*, 1982; Raghavan *et al.*, 1982; van der Werf-Messing and Hop, 1982; van der Werf-Messing *et al.*, 1984).

The results of orchiectomy and retroperitoneal irradiation for patients with clinical stage IIA NSGCTT were poor. Half of the patients developed recurrent disease, usually in the lung, and the 5-year survival rate was only 64%. The major problem was haematogenous metastasis, not tumour radioresistance. Radiotherapy failed to control retroperitoneal lymph node disease in only two patients. The results of pre-operative radiotherapy prior to retroperitoneal lymph node dissection demonstrated that relatively modest doses of radiation could eradicate nodal metastases from NSGCTT (Hussey *et al.*, 1977). The radiosensitivity of NSGCTT is probably volume-dependent (Tyrrell and Peckham, 1976). Retroperitoneal metastases less than 2 cm in diameter respond very much better to radiation therapy than does bulky abdominal disease. If radiotherapy can be shown to be effective against demonstrable disease, then there is no reason to doubt its effectiveness against micrometastatic disease in the retroperitoneal nodes.

A significant proportion of patients with clinical Stage I NSGCTT have occult micrometastatic disease within the retroperitoneal nodes. Several series have now been published on patients who had CT scanning of the abdomen followed, within 2 weeks, by excision and pathological examination of the retroperitoneal nodes (Williams *et al.*, 1980; Dunnick and Javadpour, 1981; Ehrlichman *et al.*, 1981; Richie *et al.*, 1982; Rowland *et al.*, 1982). These series dealt with a total of 192 patients. The overall accuracy of CT scanning, assessed against the pathological examination of the retroperitoneal nodes, was 73%. The false positive rate was 14%; the false negative rate was 35%. Some of the false negative results obtained with abdominal CT scanning will be eliminated if the results of lymphography are taken into consideration. Nevertheless, lymphography also has an appreciable false negative rate, probably about 25% (Peckham and Barrett, 1981).

Tumour marker estimations cannot be relied upon to compensate for the false negative results of diagnostic imaging. Twenty-five per cent of patients with active metastatic NSGCTT have been reported to have normal serum levels of alphafetoprotein and human chorionic gonadotrophin (Bosl *et al.*, 1983).

The present series confirms the excellent survival rate for adequately staged patients with clinical Stage I NSGCTT treated with orchiectomy followed by retroperitoneal irradiation. The 94.2% survival rate in the 52 Stage I patients who had lymphography is almost identical to the 97% 5-year survival rate in a similar group of patients reported from Rotterdam (van der Werf-Messing and Hop, 1982). These results are much better than the 70% 5-year survival rate after radiotherapy quoted, for comparative purposes, in the report from Manchester on their surveillance study (Read *et al.*, 1983) or the 82% survival rate for Stage I teratoma treated at the Royal Marsden Hospital between 1962 and 1975 (Peckham and Barrett, 1981).

It is usually assumed that patients who relapse after radiotherapy for NSGCTT should be treated with chemotherapy. However, 5 of 11 patients with Stage I disease who relapsed were successfully treated with further radiotherapy. Too few patients were treated with chemotherapy after prophylactic irradiation to permit any useful conclusions about toxicity produced from the interaction between radiotherapy and chemotherapy.

Of the 69 patients with Stage I disease, 9 (13%) relapsed in the lung. Very few patients in the current series had CT scanning of the chest before treatment. In a series of 21 patients with Stage I NSGCTT, staged at the Royal Marsden Hospital on the basis of chest X-ray, conventional whole lung tomography and lymphography, CT scanning detected pulmonary metastases in 4 (19%) (Husband, 1981). It is probable, therefore, that the overall relapse rate in the Edinburgh patients with Stage I disease treated since 1973 would have been reduced to between 10 and 15% had CT scanning been available. This would translate into a relapse-free survival rate of 85 to 90% and an overall survival rate of approximately 97%. These estimated figures are in close agreement with the 88% relapse-free survival rate observed in the DATECA study for patients (whose staging had included CT) with Stage I NSGCTT treated with prophylactic radiotherapy to the retroperitoneum (Schultz *et al.*, 1984). The overall relapse rates in this randomised study are 8/66 for irradiated patients and 18/66 for patients treated with orchiectomy alone. All patients who relapsed were treated successfully with chemotherapy. It is important to note that in this study 15% of the patients in the surveillance arm relapsed in the retroperitoneum. In the two UK surveillance studies (Peckham *et al.*, 1983; Read *et al.*, 1983) about 10% of patients relapsed in the retroperitoneum. None of the 66 patients randomised to receive prophylactic irradiation in the DATECA study suffered retroperitoneal relapse (Schultz *et al.*, 1984). This again demonstrates the effectiveness of radiotherapy in eradicating retroperitoneal micrometastases.

The morbidity of prophylactic radiotherapy to the retroperitoneal nodes is relatively low. The treatment itself is inconvenient rather than toxic and many patients are able to continue full-time working during treatment. The long-term morbidity is minimal. A two-fold increase in second (non-testicular) malignancies has been reported following radiotherapy for testicular cancer (Hay *et al.*, 1984). Most of these second tumours were low grade transitional cell carcinomas of the bladder or lung cancers. There was no detectable increase in the incidence of leukaemia or lymphoma.

Radiotherapy to the retroperitoneal nodes certainly compromises fertility. It is now possible, with careful shielding, to keep the dose to the remaining (putatively normal) testis to less than 1% of the given dose (Kubo and Shipley, 1982). Such a reduction in testicular dose should produce temporary aspermia rather than permanent sterility (Rowley *et al.*, 1974; Ash, 1980).

A policy of surveillance, with chemotherapy for relapse, implies treating a greater number of patients with chemotherapy than does a policy of prophylactic radiotherapy for Stage I NSGCTT. The immediate morbidity of cytotoxic chemotherapy is a serious problem. The long-term effects of retroperitoneal irradiation are well known; those of chemotherapy are less well defined but may be a cause for concern (Vogelzang *et al.*, 1980; Mead *et al.*, 1983; Meijer *et al.*, 1983; Hoekman *et al.*, 1984).

It is concluded that the high incidence of metastases beyond the retroperitoneum (particularly lung metastases) in patients with $T > 1$ primary tumours indicates that these patients should not be treated with prophylactic radiotherapy. Alternative policies could be considered for evaluation in specialised centres: either a policy of surveillance (with chemotherapy for relapse) or a policy of immediate adjuvant chemotherapy after orchiectomy.

Patients with Stage IIA disease should receive chemotherapy as initial treatment. Supplementary radiotherapy may also be indicated if there is doubt as to whether there is persistent retroperitoneal disease.

Radiotherapy to the retroperitoneum in patients with Stage I NSGCTT and T1 primary tumours will produce excellent survival with minimal morbidity.

Studies of surveillance after orchiectomy, with chemotherapy for patients who relapse, show preliminary results suggesting that this approach may produce survival equivalent to that after prophylactic radiotherapy or retroperitoneal node dissection. Follow-up times in surveillance studies have been short compared with those in the published studies on prophylactic radiotherapy. Until it is shown that the long-term survival in surveillance studies is equivalent to that of patients treated with radiotherapy after orchiectomy, it would still seem reasonable to irradiate the retroperitoneum prophylactically in patients with Stage I NSGCTT and T1 primary tumours.

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The Authors

W. Duncan, FRCPE, FRCSE, FRCR, FACR(Hon), Professor of Radiotherapy, University of Edinburgh; Honorary Consultant Radiation Oncologist, Western General Hospital and Royal Infirmary, Edinburgh.

A. J. Munro, BSc, MRCP(UK), FRCR, formerly Clinical Lecturer, Department of Clinical Oncology, Western General Hospital and Royal Infirmary, Edinburgh. Now Consultant Radiotherapist and Oncologist, Hammersmith Hospital and St Mary's Hospital, London; Honorary Senior Lecturer, Royal Postgraduate Medical School, London.

Requests for reprints to: A. J. Munro, Department of Radiotherapy and Oncology, St Mary's Hospital, Praed Street, London W2 1NY.

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Cisplatin Combination Chemotherapy for Advanced Germ-cell Testicular Tumours

R. E. TAYLOR, W. DUNCAN, P. DAVEY, A. J. MUNRO and M. A. CORNBLEET

Department of Clinical Oncology, Western General Hospital, Edinburgh

Summary—Thirty-six patients with advanced non-seminomatous germ-cell testicular tumours and two patients with advanced seminomas were treated with cisplatin-containing combination chemotherapy. Thirty-four patients received cisplatin 100 mg/m^2 iv, vinblastine 0.3 mg/kg iv and bleomycin 30 mg iv (PVB) and three patients received this combination with etoposide (VP16-213) 120 mg/m^2 iv on 3 consecutive days substituted for vinblastine (BEP). One patient received cisplatin and bleomycin only. All 35 evaluable patients with non-seminomatous tumours responded; 22 patients (61%) achieved a complete response (CR); 16 of these (73%) are alive with no evidence of disease at follow-up ranging from 18 to 55 months (median 36). Of 13 patients achieving a partial response (PR), 11 have died of progressive disease at 7 to 30 months (median 11) and two are alive with disease which has continued to regress following chemotherapy. Of 32 patients who received adequate chemotherapy, 16 (50%) are alive and disease-free and three (9%) are alive with evidence of disease.

The chances of achieving a CR were reduced in those patients with bulky disease or high levels of AFP or βhCG at presentation but not in those who had received prior radiotherapy.

Toxicity was considerable, including alopecia and nausea or vomiting in all patients, and haematological toxicity, neurotoxicity, hearing loss and dyspnoea in a substantial number of patients.

The introduction of cisplatin-containing combination chemotherapy has resulted in a marked improvement in the survival of patients with advanced germ-cell testicular tumours (Einhorn and Donohue, 1977; Stoter *et al.*, 1979; Wilkinson *et al.*, 1979; Einhorn and Williams, 1980; Samson *et al.*, 1980; Vugrin *et al.*, 1981).

Einhorn and Donohue (1977) reported the results of a series of 50 patients treated with PVB-cisplatin 20 mg/m^2 iv on days 1-5, vinblastine 0.2 mg/kg iv on days 1-2, and bleomycin 30 mg iv on days 2, 9 and 16 of a 21-day cycle, with complete remissions in 35 patients (70%). When this series was updated (Einhorn, 1979), 28 patients were alive and disease-free. Similar findings have been reported from other centres using PVB (Stoter *et al.*, 1979; Wilkinson *et al.*, 1979; Samson *et al.*, 1980, 1984).

The toxicity of PVB is considerable, including alopecia, nausea, vomiting, abdominal pain, constipation, myalgia, rigors and dyspnoea. In a later randomised study (Einhorn and Williams, 1980), it was demonstrated that PVB with a reduced vinblastine dose (0.15 mg/kg days 1, 2) was equally effective. Etoposide has been shown to be active against relapsed testicular tumours (Fitzharris *et al.*, 1980) and appears to be effective in combination with cisplatin and bleomycin (BEP) with less gastrointestinal toxicity than PVB (Peckham *et al.*, 1983).

In Edinburgh during the last 3 years, we have been treating patients with PVB with modifications to the original regime described by Einhorn and Donohue (1977). Edinburgh is a regional centre,

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serving a population of approximately 1.5 million, and virtually all patients with testicular tumours who live within south-east Scotland are referred to this department. Thus this series represents a regional experience. Many of our patients have to travel long distances to receive their chemotherapy and they appreciate the reduced time spent in hospital and not being required to attend for weekly bleomycin injections. Cisplatin is given in a single 1-h infusion, with vinblastine 0.15 mg/kg on 2 consecutive days, and bleomycin 30 mg iv on day 2, omitting the doses on days 9 and 16. Recently etoposide 120 mg/m^2 iv on 3 consecutive days has been substituted for vinblastine. The results of treating patients with these combinations are reported.

Patients and Methods

Thirty-eight patients, aged between 19 and 48 years (mean 30.2), were treated between June 1980 and October 1983. No patient had received prior chemotherapy and 10 had received prior radiotherapy. The primary site was scrotal testis in 36 patients and an intra-abdominal undescended testis in one patient. One patient presented with para-aortic node, supraclavicular node and lung metastases with no evidence of a testicular primary.

Histology

Histological material was reviewed in Edinburgh and classified according to the British Testicular Tumour Panel criteria (Pugh, 1976). Details of histology are given in Table 1. Two patients had seminoma testis, and the remainder had non-seminomatous germ-cell tumours.

Table 1 Histology of 38 Patients Receiving Cisplatin Combination Chemotherapy

Histology	*No.* (%)
Malignant teratoma undifferentiated (MTU)	17 (45)
Malignant teratoma intermediate (MTI)	7 (18)
Malignant teratoma trophoblastic (MTT)	3 (8)
Mixed teratoma/seminoma	9 (24)
Seminona	2 (5)

Staging

Patients were investigated with chest radiography, lymphography, CT scan of chest and abdomen and ultrasonography if indicated. Before each cycle of chemotherapy, routine haematology, biochemistry and creatinine clearance were performed and plasma alphafetoprotein (AFP), human chorionic gonadotrophin, β subunit (βhCG) and lactate dehydrogenase (LDH) were assayed.

The Royal Marsen Hospital staging system was employed (Table 2) (Peckham, 1981). Patients with a node mass exceeding 5 cm in diameter, or a lung metastasis exceeding 2 cm in diameter, were considered to have bulky disease and according to these criteria 25 of the 36 patients (69%) with non-seminomatous tumours and both patients with seminoma had bulky disease.

Table 2 Royal Marsden Hospital Staging Classification

Stage I	No evidence of disease outside the testis
Stage II	Infradiaphragmatic node involvement This is subdivided according to the maximum diameter of metastases into the following substage categories: IIA Maximum diameter of metastases <2 cm IIB Maximum diameter of metastases 2-5 cm IIC Maximum diameter of metastases >5 cm
Stage III	Supra and infradiaphragmatic lymph node involvement. This is subdivided as follows: Abdominal nodes: A, B, C as for Stage II Mediastinal nodes noted M+ Neck nodes noted N+ 0 = Negative lymphogram and abdominal CT scan
Stage IV	Extension of tumour to extralymphatic sites. The following suffixes define the extent and volume of metastatic spread: 0, A, B, C for abdominal nodes as for Stages I and II Mediastinal nodes noted M+ Neck nodes noted N+ Lung substage L_1 Metastases $\leqslant 3$ in number L_2 Metastases >3 in number <2 cm maximum diameter L_3 Metastases >3 in number >2 cm maximum diameter H+ Hepatic involvement Other sites, *e.g.* bone and brain, are specified.

Of the 36 patients with non-seminomatous tumours, three were Stage II, two were Stage III and 31 Stage IV. Two had liver metastases and one had brain metastases at presentation.

Tumour markers

Serial estimations of AFP, human chorionic gonadotrophin, βhCG (Kohn and Raghavan, 1981) and LDH (Von Eyben, 1978) were performed during

Table 3 Incidence of Elevated Tumour Marker Levels in 36 Patients with Non-seminomatous Tumours

Marker	*No.*	%
AFP alone	3	8
βhCG alone	2	6
LDH alone	8	22
AFP + βhCG	2	6
AFP + LDH	2	6
βhCG + LDH	7	19
AFP + βhCG + LDH	9	25
Marker positive	33	92

chemotherapy and follow-up. Table 3 shows the incidence of marker positivity in the 36 patients with non-seminomatous tumours. Thirty-three patients (92%) had at least one elevated marker. The assay of LDH increased the proportion of positive markers from 70% using only AFP and βhCG to 92%.

Drugs and doses

(a) *PVB*

Day 1 vinblastine 0.15 mg/kg iv
Day 2 vinblastine 0.15 mg/kg iv
bleomycin 30 mg iv
cisplatin 100 mg/m^2 in 500 ml 10% mannitol over 1 h with pre- and post-hydration q 21 days.

(b) *BEP*

Day 1 etoposide 120 mg/m^2 iv
Day 2 etoposide 120 mg/m^2 iv
bleomycin as for PVB
cisplatin as for PVB
Day 3 etoposide 120 mg/m^2 iv q 21 days

Twenty-nine patients received PVB, three received BEP and five were treated initially with PVB and later changed to BEP. One patient received a combination of cisplatin and bleomycin, the vinblastine being omitted owing to persistent leukopenia following radiotherapy.

High dose metoclopramide (100 mg iv infusion 2-hourly for 5 doses starting 1 h before the cisplatin infusion) was routinely used as an anti-emetic.

Response criteria

(a) *Complete response* (*CR*)

Complete disappearance of all clinical, radiological and biochemical evidence of disease, including the return to normal of elevated levels of AFP, βHCG and LDH.

(b) *Partial Response* (*PR*)

A decrease of 50% or more in the size of the products of maximum perpendicular diameters of all measurable lesions, with no evidence of progression of any lesion and without the appearance of any new lesion. The response must last at least 4 weeks.

Results

Both patients with seminoma responded. One patient with Stage IV 0 L3M + disease achieved a PR, and following mediastinal radiotherapy he has remained well and free of disease 34 months after commencing chemotherapy. The other patient, with a bulky seminoma arising in an undescended intra-abdominal testis, achieved a CR and is disease-free at 13 months.

Of the 36 patients with non-seminomatous tumours, one patient with advanced Stage IV CL3N + H + disease died of ventilatory failure and septicaemia 3 weeks after starting chemotherapy. Thirty-five patients were assessable for response.

All patients responded to chemotherapy, with 22 (63%) achieving complete remission (overall CR rate 61%).

Response according to site of disease

Table 4 shows the proportions of each site of metastasis achieving CR. Patients with lung metastases or involved neck nodes responded better (80% CR) than those with retroperitoneal nodes (64% CR).

Table 4 Complete Response (CR) According to Metastatic Site (Non-seminomatous Tumours)

Site of metastases	*No.*	*CR* (%)
Lung metastases	28	22 (79)
Mediastinal nodes	3	2
Neck nodes	12	10 (83)
Abdominal nodes	28	18 (64)
Liver metastases	2	1

Response according to bulk of disease

Table 5 shows the proportion of site achieving CR, subclassified according to bulk of disease. Of the 24 patients with bulky disease, 13 (54%) achieved CR, whereas of 11 patients with non-bulky disease, nine (82%) achieved CR; this is not statistically significant because of the small numbers in these groups ($\chi^2 = 2.479$, $P < 0.25$). Of the two patients with non-bulky disease who failed to achieve CR, one had

Table 5 Complete Response (CR) According to Site and Bulk (Non-seminomatous Tumours)

Site		*No.*	*CR* (%)
Lung metastases	Bulky	9	4 (44)
	Non-bulky	19	18 (95)
Neck nodes	Bulky	6	4 (67)
	Non-bulky	6	6 (100)
Abdominal nodes	Bulky	18	9 (50)
	Non-bulky	10	9 (90)

malignant teratoma intermediate (MTI) histology, and the other had a "mixed" MTI/seminoma.

Response according to tumour marker level

Table 6 shows the CR rate according to tumour marker level. Of the eight patients with very high levels of marker (AFP > 500 u/ml and/or βhCG > 50,000 mIu/ml), three (38%) achieved CR. Of the remaining 27 patients, 19 (70%) achieved CR. ($\chi^2 = 2.861$, $P < 0.1$).

Table 6 Complete Response (CR) According to Level of Tumour Marker (Non-seminomatous Tumours)

Tumour marker level	*No.*	*CR* (%)
AFP > 500 u/ml and/or βhCG > 50,000 mIu/ml	8	3 (38)
AFP < 500 u/ml and βhCG < 50,000 mIu/ml	27	19 (70)

Table 7 shows the CR rate according to bulk of disease and marker level. The highest CR rate was seen in those with non-bulky disease and AFP < 500 u/ml and βhCG < 50,000 mIu/ml, with eight of nine patients (89%) achieving CR. Of the six patients with bulky disease and AFP > 500 u/ml and/or βhCG > 50,000 mIu/ml, only two (33%) achieved CR ($P < 0.1$).

Table 7 Complete Response (CR) According to Bulk of Disease and Tumour Marker Level (Non-seminomatous Tumours)

Marker level	*Bulk of disease*	*No.*	*CR* (%)
AFP > 500 µl and or/ βhCG > 50,000 mIu/ml	Bulky	6	2 (33)
	Non-bulky	2	1 (50)
AFP < 500 µl/ml and βhCG < 50,000 mIu/ml	Bulky	18	11 (61)
	Non-bulky	9	8 (89)

Response according to previous radiotherapy

Details of response according to prior radiotherapy to the retroperitoneum are given in Table 8. Of the 10 patients who had received prior radiotherapy, seven (70%) achieved CR, whereas of 25 who had not received prior radiotherapy 15 (60%) achieved CR ($\chi^2 = 0.305$, $P > 0.5$).

Table 8 Complete Response (CR) According to Previous Radiotherapy (RT) to Retroperitoneum (Non-seminomatous Tumours)

	No.	*CR* (%)
Previous RT	10	7 (70)
No previous RT	25	15 (60)
Total	35	22 (63)

Response according to histology

Table 9 shows the proportions of patients with each histological subtype of tumour achieving CR.

Table 9 Complete Response (CR) According to Histology (Non-seminomatous Tumours)

Histology	*No.*	*CR* (%)
MTU	16	12 (75)
MTI	7	5 (71)
MTT	2	0
Mixed teratoma/seminoma	9	4 (44)

Overall survival

Of the 22 patients achieving CR, 16 (73%) are alive with no evidence of disease at follow-up ranging from 18 to 55 months (median 36). One patient relapsed with rapidly progressive liver metastases and died 9 months after treatment. Another patient, who was treated with cisplatin and bleomycin only, relapsed and died at 12 months. A further patient, who refused further chemotherapy after 2 cycles, relapsed and died at 25 months. A patient who presented with extragonodal MTU relapsed and died at 17.5 months, and a patient who developed acute tubular necrosis following his first cycle of PVB and could not receive further cisplatin relapsed and died at 12.5 months. One patient has relapsed at 22 months with intra-abdominal disease and is receiving further chemotherapy.

Of the 13 patients who achieved PR, two are alive and well at 19 and 26 months with small residual abdominal CT abnormalities which have continued to regress following chemotherapy. Eleven patients have died of progressive disease at 7 to 30 months (median 11).

Of 32 patients who received adequate chemotherapy, 16 (50%) are alive and disease-free at 18 to 55 months, and three (9%) are alive with evidence of disease at 19 to 26 months.

Toxicity

One patient died of ventilatory failure 3 weeks after starting chemotherapy. Thirty-seven patients were assessable for toxicity (Tables 10 and 11).

All patients experienced alopecia and gastrointestinal toxicity, sufficiently severe for one patient to refuse chemotherapy after 2 cycles.

Table 10 Non-haematological Toxicity of PVB and BEP

Toxicity		*No.*	%
†* Gastrointestinal	mild	9	24
	moderate	13	35
	severe	15	41
Diarrhoea		3	8
Constipation/abdominal pain		11	30
Paralytic ileus		2	5
Alopecia		37	100
Symptomatic lung function abnormalities		5	14
Neurotoxicity		14	38
Rigors		1	3

* Mild—nausea only. Moderate—intermittent vomiting. Severe—repeated vomiting requiring therapy.
† Of 3 patients receiving BEP 1 mild, 1 moderate and 1 severe.

Table 11 Haematological Toxicity of PVB and BEP

Toxicity	*No.*	%
Anaemia (Hb < 10 g/l	17	46
Leucopenia (WBC < 3000/cu mm)	13	35
Thrombocytopenia (platelets < 100,000/cu mm)	—	—
Patients requiring blood transfusion	15	41
Neutropenic infection	7	19

Long-term toxicity consisted of neurotoxicity in seven patients (19%), hearing loss in three (8%), dyspnoea in two (5%) and skin rash in three (8%). One patient, following his first cycle of PVB, developed acute tubular necrosis leading to chronic renal failure and haemodialysis. No patient developed serious bleomycin pulmonary toxicity.

Of the 197 cycles of chemotherapy that were administered, 21 were delayed because of myelotoxicity. In the 11 patients who had received prior radiotherapy there were 13 delayed cycles and five dose reductions, while in the 26 patients who had not received prior radiotherapy there were eight delayed cycles and one dose reduction.

Discussion

This series consisted of an unselected group of patients and represents the regional experience of treating patients with advanced germ-cell testicular tumours.

The CR rate of 61% for patients with non-seminomatous germ-cell tumours is similar to that of other reported series (Table 12) employing cisplatin-containing combination chemotherapy (Einhorn and Donohue, 1977; Einhorn, 1979; Stoter *et al.*, 1979; Wilkinson *et al.*, 1979; Einhorn and

Table 12 Results of Treatment with PVB/BEP

Series	*Reference*	*Drug combination*	*No. of patients*	*Overall CR (%)*	*% of patients with bulky disease*	*Minimal disease CR (%)*	*Bulky disease CR (%)*
Einhorn and Donohue (1977)	1	PVB	50	35 (70)	53	91	60
Stoter *et al.* (1979)	12	PVB	40	24 (60)	90	100	56
Wilkinson *et al.* (1979)	16	PVB	27	18 (67)	—	—	—
Einhorn and Williams (1980)	3	PVB	78	53 (68)	58	97	47
Samson *et al.* (1980)	10	PVB	143	84 (59)	72	85	49
Peckham *et al.* (1983)	8	BEP	36	30 (83)	53	93	86
Samson *et al.* (1984)	11	*PVB	56	35 (63)	75	79	57
Present series	—	PVB/BEP	36	22 (61)	69	82	54

* High dose cisplatin group

Williams, 1980; Samson *et al.*, 1980, 1984; Vugrin *et al.*, 1981). One series (Peckham *et al.*, 1983) reported higher CR rates. This might be explained by the relatively low proportion of patients with bulky disease in their study; in addition, a number of patients with bulky stage IV L3 H+ disease were excluded from the study and only two patients had bulky lung metastases compared with nine in the present series.

The PVB regime currently employed in Edinburgh is a modification of that of Einhorn and Donohue (1977), and the reduction in time spent in hospital by giving the cisplatin in a single intravenous infusion rather than over 5 days, together with the omission of bleomycin on days 9 and 16, are of significant benefit to our patients, many of whom travel long distances to receive their chemotherapy. These modifications do not appear to prejudice the chance of achieving CR. No patient developed serious bleomycin pulmonary toxicity.

Our results are similar to those reported by others, with the CR rate for malignant teratoma undifferentiated (MTU) being higher than for other histologies, and also a higher CR rate for lung metastases than for para-aortic node metastases and for non-bulky compared with bulky disease.

The CR rate for patients with very high levels of serum AFP and βhCG was lower than for patients with moderately raised or normal levels of these markers. The highest CR rate was seen in patients with non-bulky disease and normal or moderately raised tumour marker levels, and the lowest CR rate was seen in those with bulky disease and very high tumour marker levels. It is not possible with the numbers of patients in this study to say whether bulk or disease or tumour marker level is the most important prognostic indicator.

Prior radiotherapy as given in Edinburgh does not appear to prejudice the chance of a CR, although these patients were more likely to have cycles delayed because of haematological toxicity.

Of the 22 patients who achieved a CR, six relapsed, three of them having received inadequate chemotherapy. Of the 13 patients with non-seminomatous tumours achieving PR, two have small residual abdominal CT abnormalities which have continued to regress following chemotherapy. These might have achieved CR following surgical excision of residual masses but a policy of regular CT scanning and close clinical surveillance is employed for patients with small stable or regressing residual masses following chemotherapy and radiotherapy. In the remaining patients achieving PR, surgical resection of residual masses following chemotherapy was considered inappropriate owing to extent of disease or intercurrent medical condition. The survival of patients achieving PR was disappointing and this might be explained by the low proportion who were suitable for post-chemotherapy surgery. In one recent series (Tait *et al.*, 1984), 23.8% of patients had masses excised after treatment.

Although the CR rate for non-bulky disease is encouraging, only 54% of patients with bulky disease achieve a CR. It may be that this can be improved by increasing the number of drugs to which the tumours are exposed by alternating cycles of PVB with BEP or by using alternating non-cross-resistant combinations (Newlands *et al.*, 1983).

The current aim must be to evaluate new, more aggressive regimes of multiple drug chemotherapy in patients with those features of disease which predict a poor response to standard therapy with PVB.

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The Authors

R. E. Taylor, MRCP, FRCR, Imperial Cancer Research Fund Research Fellow and Honorary Senior Registrar, Department of Clinical Oncology, Western General Hospital and Royal Infirmary, Edinburgh.

W. Duncan, FRCPE, FRCSE, FRCP, FACR(Hon), Professor of Radiotherapy, University of Edinburgh and Honorary Consultant Radiation Oncologist, Western General Hospital and Royal Infirmary, Edinburgh.

P. Davey, MRCP, DMRT, FRCR, Clinical Lecturer, Department of Clinical Oncology, Western General Hopsital and Royal Infirmary, Edinburgh.

A. J. Munro, MRCP, FRCR, formerly Clinical Lecturer, Department of Clinical Oncology, Western General Hospital and Royal Infirmary, Edinburgh. Now Consultant Radiation Oncologist, Hammersmith Hospital and St Mary's Hospital, London.

M. A. Cornbleet, MD, MRCP, Senior Registrar, Department of Clinical Oncology, Western General Hospital and Royal Infirmary, Edinburgh.

Requests for reprints to: R. E. Taylor, Department of Clinical Oncology, Western General Hospital, Edinburgh EH4 2XU.

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The Fibrous Skeleton of the Corpora Cavernosa and its Probable Function in the Mechanism of Erection

A. M. B. GOLDSTEIN, J. P. MEEHAN, J. W. MORROW, P. A. BUCKLEY and F. A. ROGERS

Departments of Surgery (Urology) and Physiology, University of Southern California, Los Angeles, USA

Summary—The corpora cavernosa contain a fibrous skeleton composed of tunica albuginea with its fibrous columns, periarterial and perineural fibrous sheaths, and an intraparenchymal fibrous framework attached to all fibrous elements of the corpora cavernosa. This anatomical arrangement probably plays an important part in the firmness of the corpora cavernosa during erection. The fibrous framework, due to its numerous attachments to the deep surface of the tunica albuginea and its columns, when stretched during erection, prevents bending and deformation of the corpora cavernosa.

Many histologists agree that the tunica albuginea of the corpora cavernosa is constituted mainly of thick collagenous bundles and that it contains few elastic fibres (Bloom and Fawcett, 1975; Copenhaver *et al.*, 1978; Ham and Cormack, 1979). Since this tunica has to be able to expand during erection, the arrangement of the collagenous bundles has to be such as to permit such expansion. Stieve (1930) and Conti (1952) specifically mentioned that the tunica can have a thickness of 2 to 3 mm in the flaccid penis, while it would be only 0.5 mm thick during erection. The incomplete partitions separating the vascular cavernous spaces are made up of fibromuscular tissue.

Considering the great length of the corpora cavernosa in comparison with their diameter, the above descriptions would not explain how the tunica albuginea alone could oppose enough resistance against flexing and possible rupture of the corporea during erection and intercourse. The purpose of this study was to seek a better understanding of the fibrous framework of the corpora cavernosa and its possible role during erection.

Materials and Methods

The material was obtained from 17 cadavers of men aged between 17 and 97, together with specimens from another group of five men between the ages of 46 and 60 who were undergoing amputation of the penis for cancer. Slices of corpora cavernosa from cadavers of men aged 17, 53, 60, 68 and 95 were taken from both distal and proximal ends of the corpora. All slices were fixed in 10% formaldehyde and embedded in paraffin. Between 100 and 300 serial cross sections 10 microns thick were made from all specimens. From one specimen of the cadaver of a 97-year-old man longitudinal serial sections through the corpora cavernosa were also performed. Altogether 3220 sections were studied by light microscopy.

Most of the sections were stained with haematoxylin and eosin, while the remainder were stained with trichromic (Polek), elastic (Gomori) and silver (Bielschowsky) stains.

Results

The tunica albuginea is made up almost entirely of thick collagenous fibres (Fig. 1). From the deep surface of the tunica finger-like fibrous columns penetrate the substance of the corpora at different depths (Fig. 2). The thick collagenous fibres making up these columns are also undulated, as in the tunica albuginea, but the undulations are much smaller and orientated along the axis of the columns. Elastic fibres are sparse (Fig. 3).

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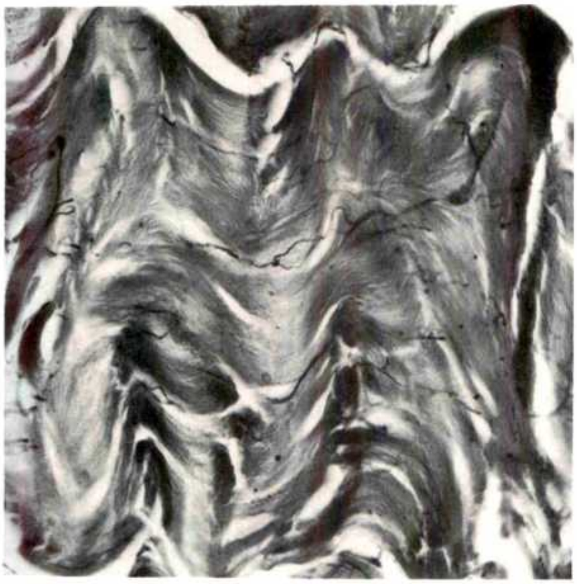

Fig. 1 Tunica albuginea seen on a cross section through the corpus cavernosum of a 56-year-old man (stained for elastic material). Note the undulations of its fibrous bundles. The fine black stained fibres are elastic. (Reduced from × 140).

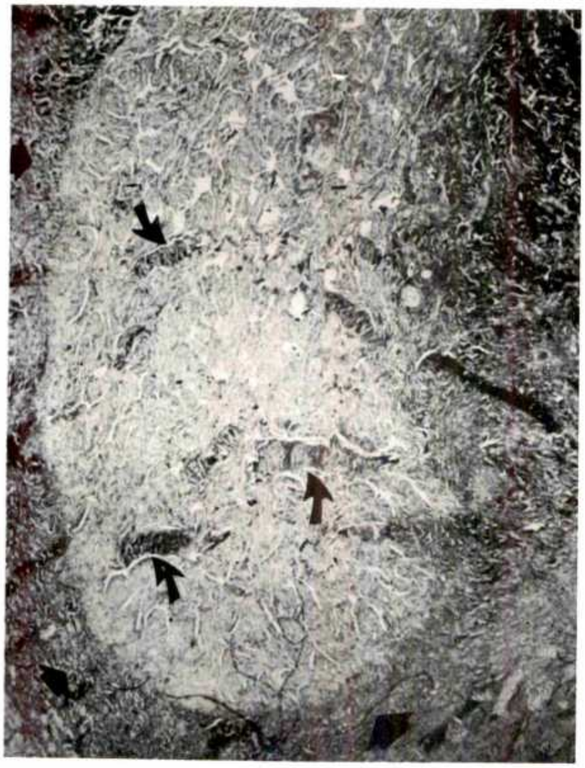

Fig. 2 Cross section through one corpus cavernosum of a 56-year-old man stained with trichromic stain. Fibrous columns penetrate deep into the parenchyma of the corpus (arrows). Tunica albuginea (arrow heads). (Reduced from × 7.5).

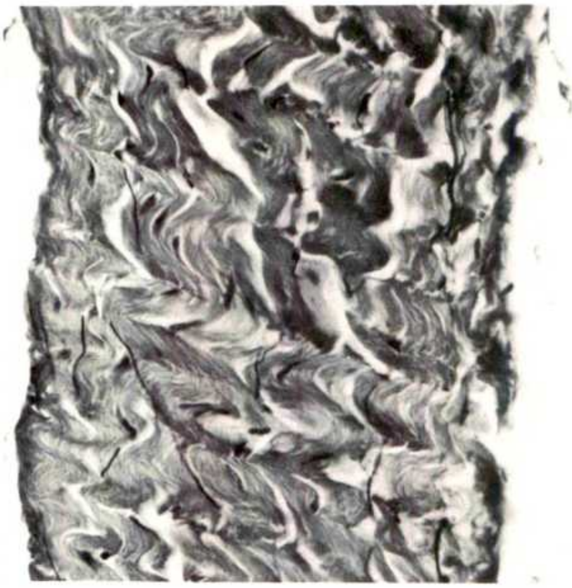

Fig. 3 Column of the tunica albuginea cut longitudinally. Stained for elastic material. Note the undulations of the fibrous bundles which run parallel to the axis of the column. The undulations are finer than in the tunica albuginea. The thin fibres stained black are elastic. (Reduced from × 140).

All intracavernosal arteries and their helicine branches are surrounded by sheaths of fibrous tissue (Goldstein *et al.*, 1982) (Fig. 4) of which the component collagenous fibres are also undulated (Fig. 5). All intracavernosal nerves are located within fibrous tunnels (Fig. 6).

A framework of fibrous bundles within the parenchyma of the corpora establishes attachments to all fibrous elements of the corpora: the deep surface of the tunica albuginea, the columns of the tunica and the fibrous sheaths of the arteries and nerves (Figs 7 and 8). This fibrous meshwork on separate sections appears interrupted and is probably the fibrous element of the parenchymal trabeculae of the corpora cavernosa.

The bulk of the parenchyma of the corpora is made up of smooth muscle arranged in bundles and inserted through their ends to the fibrous elements of the corpora cavernosa.

Discussion

Although the tunica albuginea is made up almost completely of inextensible material, it is able to expand during erection owing to the undulations of its collagenous fibres in a state of flaccidity. The fibres making up the intracavernosal fibrous framework will also be stretched until the fibres become

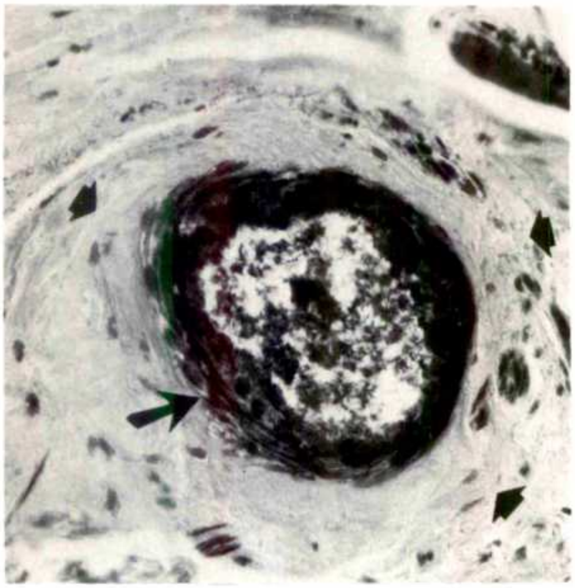

Fig. 4 Cross section through a helicine artery (arrow) surrounded by a fibrous sheath (arrow heads). Haematoxylin and eosin stain. (Reduced from × 70).

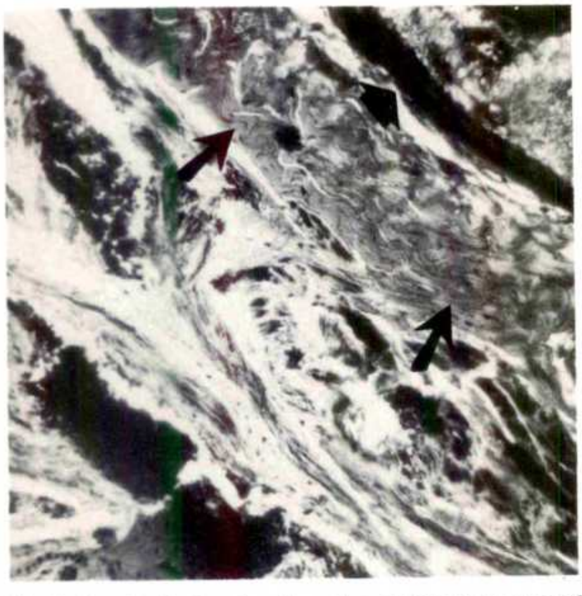

Fig. 5 Longitudinal section through a corpus cavernosum of the cadaver of a 97-year-old man. Trichromic stain. Central artery longitudinally sectioned (arrow head). Note the fibrous sheath surrounding the central artery and the undulating collagenous fibres of the collagenous sheath (arrows). (Reduced from × 70).

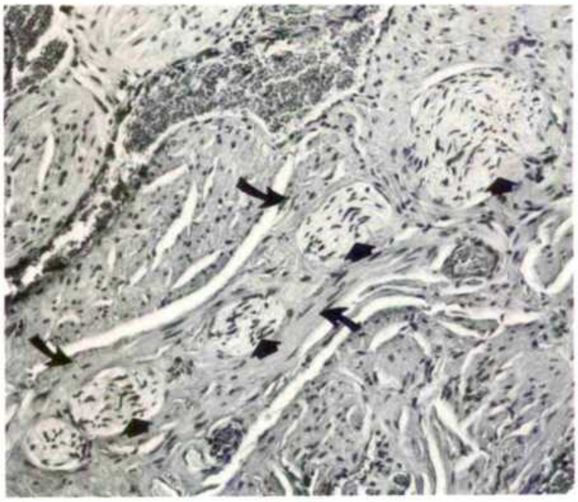

Fig. 6 Intracavernosal nerve surrounded by a fibrous sheath. Cross section through the corpora cavernosa of a 46-year-old man. Haematoxylin and eosin stain. Longitudinal section through the undulated nerve (arrow heads). Fibrous sheath surrounding the nerve (arrows). (Reduced from × 58).

straight. The sparse elastic fibres may help the collagenous fibres of all fibrous elements to regain their undulations in flaccidity. Because of a similar anatomical arrangement the fibrous columns of the tunica can elongate during the expansion of the corpora cavernosa in erection (Fig. 3). Numerous fibres of the intracavernosal framework are solidly attached to these columns (Fig. 7) and the latter can often establish direct attachments to the fibrous sheaths surrounding the arteries (Goldstein *et al.*, 1982) (Figs 9 and 10).

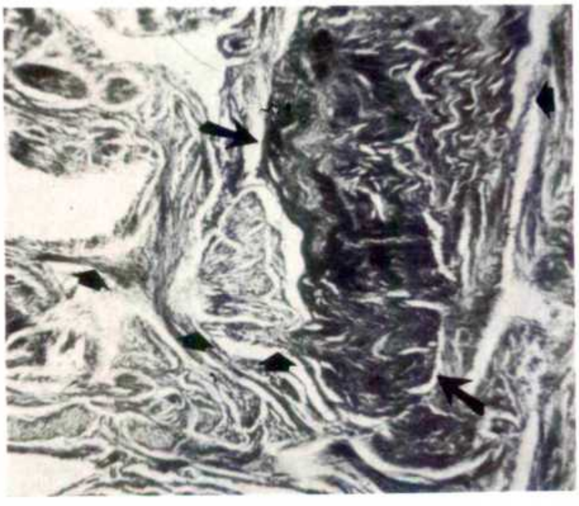

Fig. 7 Tip of a fibrous column of the tunica albuginea (arrows) of a 56-year-old man. Trichromic stain. Note collagenous fibres from the parenchyma of a corpus cavernosum attached to the column (arrow heads). (Reduced from × 80).

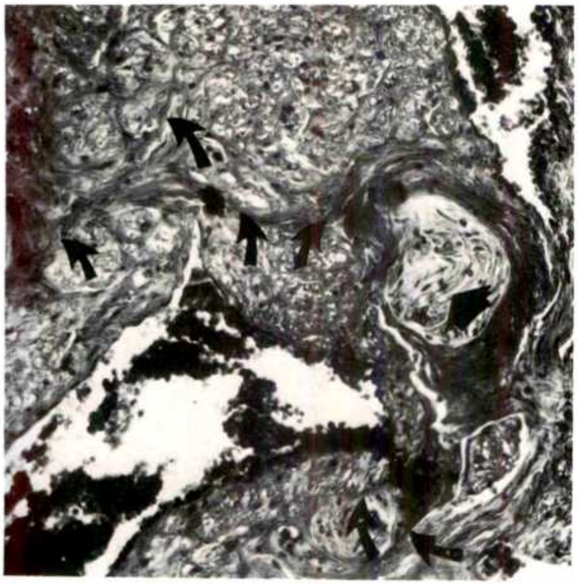

Fig. 8 Intracavernosal nerve obliquely sectioned (arrow head) surrounded by a thick fibrous sheath to which bundles of fibres of the intracavernosal framework are attached (arrows). Trichromic stain. (Reduced from × 60).

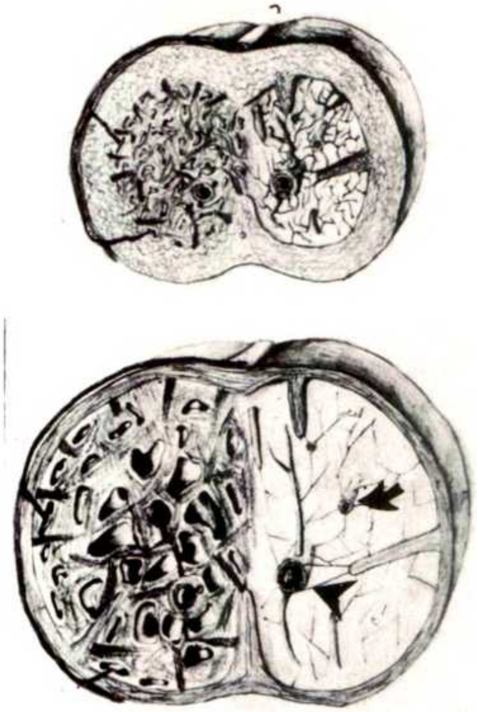

Fig. 10 Diagram showing the same cross sectioned slice of a corpus cavernosum in flaccidity and erection: flaccid (top), erected (bottom). Note how during erection the tunica albuginea becomes much thinner than in flaccidity and its undulating collagenous fibres lose their waviness. The columns of the tunica are also more elongated in erection. Note also the difference between the intracavernosal framework in the right half of each figure. In the erect penis the framework is stretched and its bundles of fibres attached to all fibrous elements of the corpora, including the fibrous sheaths of the arteries and nerves, are pulling the latter from all directions. Central artery in its fibrous sheath (arrow head). Nerve in its fibrous sheath (arrow).

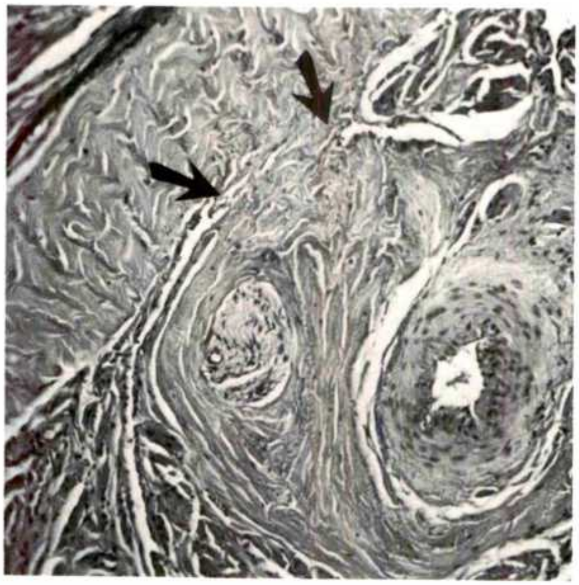

Fig. 9 Intracavernosal central artery, cross sectioned, surrounded by its fibrous sheath. The latter is directly attached to a column of the tunica albuginea (arrows). Haematoxylin and eosin stain. (Reduced from × 50).

The fibres of the intracavernosal fibrous framework are relaxed in the flaccid penis and become stretched when the penis is erect.

Since the intracavernosal pressure during erection is highly elevated (Jevtich, personal communication; Meehan and Goldstein, 1983), the arteries and nerves would probably be unable to function if they were not surrounded by fibrous sheaths to which the bundles of fibres of the fibrous framework are attached. This anatomical arrangement probably prevents the collapsing of arteries and the compression of nerves during erection, when the elements of the fibrous framework stretch (Goldstein *et al.*, 1984). In this latter condition the fibrous bundles of the intracavernosal framework pull on the fibrous sheaths around the arteries and the nerves from all directions while being stretched by the distension of the tunica albuginea and its columns during the filling of the vascular spaces of the corpora when erected.

Without the parenchymal framework attached to all fibrous elements of the corpora, and especially to the deep surface of the tunica albuginea, it is difficult to conceive how the corpora, relatively thin structures compared with their length, would resist flexing and frequent ruptures during erection and intercourse.

Hollow but relatively thin metallic columns require an inside metallic framework to increase their resistance to bending and breaking (Haertlein, 1958). The corpora cavernosa are thin, long bodies that, in a similar manner, have an internal framework made up of the intracavernosal fibrous elements. Any distortions or later bulgings of the corpora may be due to rupture of these elements and possibly subsequent faulty repair.

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The Authors

A. M. B. Goldstein, MD, Adjunct Professor of Surgery (Urology).
J. P. Meehan, MD, Professor of Physiology and Biophysics.
J. W. Morrow, MD, Professor of Surgery (Urology).
P. A. Buckley, Histology Technician.
F. A. Rogers, Histology Technician.

Requests for reprints to: A. M. B. Goldstein, Department of Surgery (Urology), University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033, USA.

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Toxicity Testing of Urinary Catheters

M. TALJA, L. C. ANDERSSON, M. RUUTU and O. ALFTHAN

Second Department of Surgery/Urological Unit, Helsinki University Central Hospital; University Department of Pathology, Helsinki, Finland

Summary—The tissue toxicity of 23 urinary catheter batches (6 latex and 2 non-latex brands) was tested *in vitro* and *in vivo*. *In vitro*, a human T-cell leukemia line (JM) was cultured in the presence of different concentrations of eluates made from the catheters. The cytotoxicity of the eluates was assessed from their ability to inhibit DNA synthesis measured by incorporation of ^{3}H-thymidine. *In vivo*, two methods were used. Strips of catheters were implanted into the rabbit dorsal muscle and pieces of catheters were implanted into the rat peritoneal cavity. After four days, the foreign body reaction, type of inflammation and necrosis were quantified macroscopically and by light microscopy.

The results of the *in vitro* cytotoxicity test were correlated with those of *in vivo* methods. The rat peritoneal implantation test correlated better with the cell culture test ($P<0.01$) than with the rabbit muscle implantation test ($P<0.05$). Based on the clinical experience of urethral stricture complications caused by urinary catheters, catheters yielding eluate which at 30% dilution inhibited 50% DNA synthesis were regarded as toxic. According to this, the rabbit muscle implantation test was not reliable in testing the tissue toxicity of urinary catheters, while the cell culture test was quantitative and seemed to correlate with both the rat peritoneal implantation test and with the clinical complications observed.

Several epidemics of urethral stricture associated with the short-term use of latex catheters have been reported (Frazer *et al.*, 1982; Ruutu *et al.*, 1982; Smith and Neligan, 1982; Wesley-James, 1982; Sutherland *et al.*, 1983). Our attention was aroused by the fact that there are no international standards for tissue toxicity testing of urinary catheters. The manufacturers themselves are responsible for the testing procedures, but such testing might in some cases be insufficient (Ruutu *et al.*, 1985). Another problem is the poor clinical recording of the catheter brands used. Only the size of catheter is usually mentioned, and it is difficult to associate urethritis or stricture formation with a particular brand or batch of catheter retrospectively. Urologists usually consider that such post-catheterisation strictures are caused by mechanical trauma, assuming that the catheters themselves are inert devices.

The recommended method for tissue toxicity testing of urinary catheters is the rabbit muscle implantation test (US Pharmacopeia XX, 1980). Several manufacturers have also used modern cell culture methods. In addition, the mice systemic toxicity test is still being used by some manufacturers as the only method. This method has, however, proved insensitive (Graham *et al.*, 1983). Cell culture tests are known to be sensitive and easily reproducible, but their clinical relevance has been questioned (Engel, 1983). Autian (1973) emphasised that the tissue toxicity test employed should be relevant for the clinical use of the medical device. He suggested "cumulative toxicity" based on *in vitro* and *in vivo* tests. So far, however, clinically relevant toxicity limits for single tests have not been established.

In this study we have compared an *in vitro* cell culture test with *in vivo* animal tests, a rabbit muscle implantation test and a new rat peritoneal

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implantation test (Talja, 1985), and corrected these tests with the clinically recorded urethral stricture complications caused by these catheters.

Material and Methods

Thirty-one batches of catheters were tested: the rat peritoneal implantation test was performed on 31 batches, the rabbit muscle implantation test on 24 and the cell culture test on 29. Twenty-three batches were tested by all methods. The catheters were from six latex and two non-latex brands. A silicone catheter brand was used as a negative control, since it was known to have no clinical side effects (Ruutu *et al.*, 1982) and was shown to be non-toxic in the cell culture test (Ruutu *et al.*, 1985).

(*i*) *Rabbit muscle implantation test*

The test was performed according to the US Pharmacopeia XX (1980). Four test and two control strips of catheters were implanted into the dorsal muscle of rabbits for 4 days. Unlike the original model, the results were evaluated histologically (Autian, 1973; Wilsnack, 1976; British Standards, 1981; Graham *et al.*, 1983).

Changes in tissue toxicity were classified according to tissue necrosis (grade 0-3) and inflammatory cell infiltration (grade 0-3). The type of inflammatory cells was also recorded. The tissue toxicity value of the control strips was subtracted from the corresponding value of the test strips, and the values of animal pairs with the same test material were added together (sum of the grades 0-12). Macroscopic findings were also observed and recorded.

(*ii*) *Rat peritoneal implantation test*

The test is based on the inhibition of the rat peritoneal foreign body reaction. Test and control catheter pieces 3 cm in length were implanted into the rat abdominal cavity for 4 days. The invasion of the peritoneal foreign body reaction into the lumen of the catheter pieces was classified macroscopically (grade 0-4) and evaluated microscopically. The test was performed by using six rats for each catheter studied (sum of grades 0-24) (Talja, 1985).

(*iii*) *Cell culture test*

The test was performed by using an accepted cell culture technique with human cell lines. Of the six cell lines tested, T-cell leukemic cells (JM) were considered the most suitable because of their constant proliferation properties. Catheters were eluated in 30 ml RPMI-1640 culture medium. Dilutions of the eluates, 100%, 30%, 3%, 1%, 0.3% and 0.1%, were added to the cell cultures. The cells were cultured for 2 days, and 6 h before the termination of the cultures ^{3}H-thymidine was added. DNA synthesis was determined in triplicates and compared with control catheters not containing eluates (Ruutu *et al.*, 1985).

(*iv*) *Statistical design*

In the statistical calculations the significance of differences in the rat peritoneal implantation test was studied by the Kruskal-Wallis one-way variance test: 0.95 was selected as the probability that no non-toxic catheter would be rejected, *i.e.* Bonferroni correction was used to make multiple testing reliable.

Correlation between the results obtained by the rat peritoneal implantation test, the rabbit muscle implantation test and the cell culture test was suited by drawing regression curves. The sensitivities of the different methods on the basis of the curves were compared. The results of the rat peritoneal implantation test and the rabbit muscle implantation test were used as such in the comparison, while those of the cell culture method were transformed to LD$_{50}$ values. This concept, which is well known in medical industry, has not, to our knowledge, been used in the toxicity testing of medical devices, but it proved most suitable for this purpose. LD$_{50}$ values were estimated mathematically from the following equation:

$$y = \frac{1}{p_1 e^{p_2 \ln x} + p_3}$$

y = degree of inhibition in DNA synthesis
x = eluate concentration
p_1, p_2, p_3 = constants describing the shape of the curve. These variables were estimated separately for each individual catheter.

Results

(*i*) *Rabbit muscle implantation test*

The microscopic and macroscopic findings were roughly in agreement. The differences between the catheters were more prominent in the histological classification. As a sign of local irritation, dystrophic calcifications were seen around the strips of some batches. Local eosinophilia, 80% of the inflammatory cells, was also seen around some catheter implants. Tissue necrosis was observed only around implants of the most toxic batches. In testing the same catheter batch, differences were also found between animal pairs. These test results of animal pairs were between 0 and 6 (scale 0-12).

(*ii*) *Rat peritoneal implantation test*

The degree of foreign body reaction around and in the lumen of 3-cm pieces of catheter was macroscopically evaluated after a 4-day implantation period. The lumina of the non-toxic pieces were filled with vascularised granulation tissue. The lumina of catheters showing high toxicity in the cell culture test were completely empty. The test results varied evenly between 4 and 22 in the scale (0-24).

Three catheter brands induced intraperitoneal adhesions. Histological evaluation revealed heavy granulocyte infiltration of the contact sites between the peritoneum and omentum to the outer surfaces of the catheters. These same catheter brands also caused the eosinophilic reaction in the rabbit muscle implantation test described above.

(*iii*) *Cell culture test*

The degree of inhibition of the DNA synthesis in cultures supplemented with various dilutions of catheter eluates was expressed as a percentage of DNA synthesis in control cultures. A great variation from 1.4 to 80% was seen in the values of 50% inhibition in the DNA synthesis (LD_{50} value) between catheters. The LD_{50} value could not be determined in four catheters because they were completely non-toxic. In 14 catheters the eluate concentration below 30% caused 50% inhibition in the DNA synthesis (LD_{50} value). This value was chosen according to the clinical side effects as the toxicity limit in this test.

(*iv*) *Correlation between different tests*

According to correlation diagrams, linear correlation was observed between all test methods: rat peritoneal implantation test/cell culture test, significant ($P<0.01$, Fig. 1a); rabbit muscle implantation test/cell culture, almost significant ($P<0.05$, Fig. 1b); rat peritoneal implantation test/rabbit muscle implantation test, almost significant ($P<0.05$, Fig. 1c). Interbrand, interbatch in the same brands, and also intrabatch variation was observed in the toxicity tests (Table).

Based on our clinical experience of urethral stricture complications, a 30% dilution was chosen as the limit of LD_{50} toxicity in the cell culture test. The corresponding toxicity limits were obtained from the correlation diagrams: the rabbit muscle implantation test 2.5 (Fig. 1b) and the rat peritoneal implantation test 8.5 (Fig. 1a).

The cell culture test was the most sensitive. In this test 14/29 catheters were toxic, whereas 9/31 were regarded as toxic in the rat peritoneal implantation test and 5/24 in the rabbit muscle implantation test. These toxic batches were from 5/6 latex brands. Two batches were regarded as toxic by all test methods. Five batches were regarded as toxic by two methods and six by one method (Table).

In the rat peritoneal implantation test 7/31 catheters were abandoned as toxic with Bonferroni corrected *P* value <0.05.

Table Results of Toxicity Testing (Mean of each Test is 50). Brands A-F: Latex Catheter Brands. Brands G-H: Non-latex Brands.

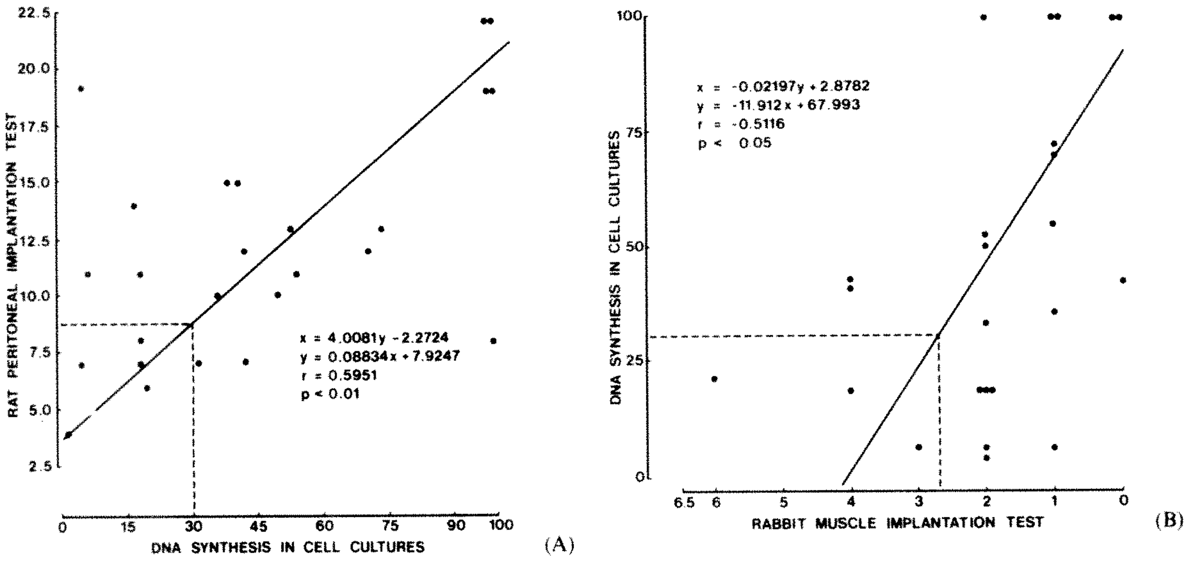
	Rabbit muscle implantation test	*Cell culture test*	*Rat peritoneal implantation test*
Brand A (9 batches)	41	20*	33* **
	−5.0*	21*	25* **
	13*	44	63
	13*	47	29* **
	41	57	54
	41	55	42
	41	34	29* **
	63	109	92
	63	39	42
Brand B (2 batches)	25*	4*	29* **
	41	1	17* **
Brand C (3 batches)	41	19*	29* **
	13	18*	58
	63	4*	79
Brand D (2 batches)	100	109	33* **
	63	77	50
Brand E (3 batches)	100	45	50
	41	20*	50
	41	7*	46
Brand F (2 batches)	63	80	54
	63	60	50
Brand G	40	109	79
Brand H	100	109	79

* Toxic result of a test when a 30% dilution is regarded as the baseline toxicity limit: the limit applied in the other tests in the cell culture test.

** Toxic batches in the rat peritoneal implantation test when the catheters tested were correlated with the control catheter.

Discussion

Animal testing methods for the screening of new



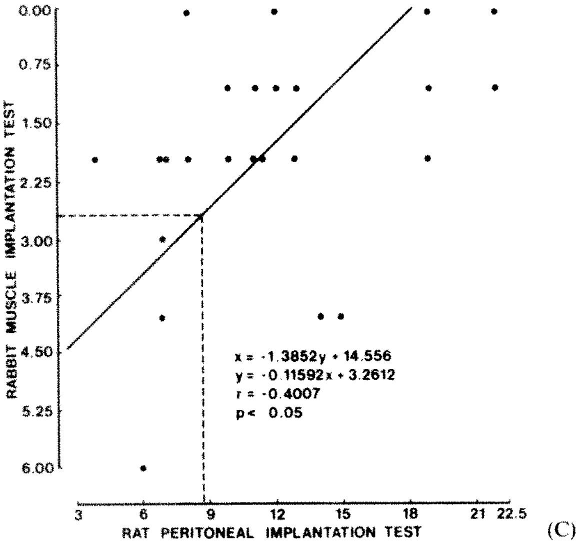


Fig. 1 Regression lines between different toxicity testing methods. (A) Inhibition of DNA synthesis in cell cultures (percentage of control)—rat peritoneal implantation test. (B) Inhibition of DNA synthesis in cell cultures—rabbit muscle implantation test. (C) Rat peritoneal implantation test—rabbit muscle implantation test. The dotted lines demarcate toxic areas according to the two test methods.

drugs and biological preparations have been regarded as an essential prerequisite to clinical trials in humans. It has been generally assumed that medical devices are mechanically and chemically stable and possibly have fewer problems in terms of tissue toxicity. However, it has been proved that certain materials may provoke local or systemic injury by virtue of biological incompatibility or by release of various substances (Engel, 1983). Latex catheters have also been shown to have tissue toxic effects (Graham *et al.*, 1983; Ruutu *et al.*, 1984). These products have, however, passed the currently accepted tissue toxicity tests of the manufacturers. Thus the following questions arise. (1) Are the tests insensitive and unsuitable for this kind of testing? (2) Is the industrial manufacturing process of latex catheters sufficiently controlled and consistent as to prevent the appearance of toxic products even in small amounts? (3) If the tests are in fact adequate, are they applied effectively enough in industry?

Since 1965 (Rosenbluth *et al.*), general toxicity, specific cell toxicity and the metabolism of components in certain tissues of medical materials have been studied by cell culture tests. These tests measure acute toxicity. Therefore the incubation times are usually short, from 30 min to 9 days (Horvarth, 1980). The reproducibility of the tests has been considered good (Wilsnack, 1976; Thelestam and Möllby, 1980; Ruutu *et al.*, 1985) but the methods are more sensitive than the animal tests (Dillingham *et al.*, 1975; Wilsnack, 1976). Methods measuring cell division are particularly sensitive (Autian, 1973; Dillingham *et al.*, 1975), and this was also shown by our results.

The results of cell culture titration showed that the shapes of the curves reflecting inhibition of the DNA synthesis were similar throughout (Fig. 2). Shifts to the right were caused by the non-toxic catheters and to the left by the toxic ones. The LD_{50} index, which best describes tissue toxicity of catheters, can be visually determined by a curve or mathematically according to the given formula.

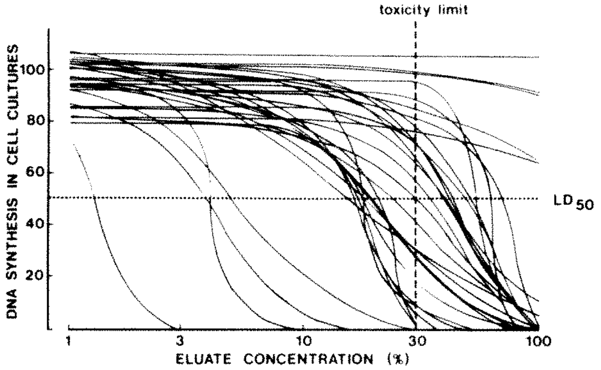


Fig. 2 DNA synthesis inhibition in cell cultures (percentage of control) as the function of catheter eluate concentration. The curves are similar in shape and have been drawn according to mathematical evaluation of the observed results. The LD_{50} index best describes the toxicity of catheters. Toxicity limit, at 30% dilution, was chosen according to clinical background.

The rabbit muscle implantation test presented by the US Pharmacopeia XX (1980) was modified. The results were evaluated histologically. The difference between the catheters was hard to classify, though the corresponding differences in the other tests were quite clear. Nearly all catheter brands had passed this test in the product quality controls of the manufacturers.

According to our findings, the results are affected by artificial haemorrhages caused by implantation. These haemorrhages on their own provoke an inflammatory reaction and granulocyte infiltration. Even a muscular jerk can cause this kind of haemorrhage under light anaesthesia and it is possible that this is the explanation for the differences between individual animals used for testing the same catheter batches.

This problem in the rabbit muscle implantation test led us to look for a new *in vivo* method for tissue toxicity testing of urinary catheters. We found that a method based on the inhibition of the rat peritoneal foreign body reaction was easy to perform and its cost was low. The evaluation of the test was based on a five-grade classification. The reproducibility of the test was good and it can be considered semiquantitative (Talja, 1985).

The unusual reactions associated with three catheter brands in the *in vivo* tests (formation of adhesions around catheter pieces in the rat peritoneal implantation test and eosinophilic granulocyte infiltration in the rabbit muscle implantation tests) were hard to explain. Obviously, the reactions were not toxic, because increased toxicity in the cell culture test was associated with decreased formation of adhesions in the rat peritoneal implantation test. These unusual reactions may be due to factors which Painter *et al.* (1971) found when they implanted catheters in the urethra of dogs and discovered that latex catheters produced extensive polymorphonuclear leucocyte infiltration in the submucosa. The reaction can also explain some clinical irritations of the urethra caused by catheters.

We studied various ways of correlating single test results together and finally chose the regression analysis. According to the regression lines, it is obvious that the rat peritoneal implantation test is better correlated with the cell culture test ($P<0.01$) than is the rabbit muscle implantation test ($P<0.05$). The other problem was to determine the toxicity limit for a single test. The most reproducible of the methods used was the cell culture test. We therefore regarded it as the basic method and concluded that catheters causing 50% inhibition of the DNA synthesis with 30% eluate concentration should be regarded as toxic, because such catheters had been involved in an epidemic of urethral strictures (Ruutu *et al.*, 1984). Graham *et al.* (1983) adopted the same limit in their work. Toxicity limits for the other tests were determined according to this value. It was found that in the regression analysis the same catheters were abandoned as in the reciprocal comparison in the rat peritoneal implantation test. Thus the toxicity limits of the two methods, one based on the clinical background and the other on theoretical statistical calculations, were in agreement. The idea of the "cumulative toxicity index" presented by Autian and Dillingham (1973) was applied in this study in a new way: the LD_{50} values of the cell culture test were used as the baseline figures with which the other methods could be co-ordinated.

Classification errors are common in the evaluation of animal tests without standardisation, when the *in vivo* methods are used by different workers. By this arrangement the *in vivo* methods can be correlated to those *in vitro*. In the evaluation of urinary catheters for tissue toxicity it is necessary to have test methods which measure acute toxicity *in vitro* and chronic toxicity *in vivo*. The new rat peritoneal implantation test appears now to be the preferred method in test protocols because the rabbit muscle implantation test has been shown to be too insensitive in tissue toxicity testing of medical devices.

Acknowledgements

We thank Dr P. Voutilainen for the statistical calculations. This study was supported by a grant from the Emil Aaltonen Foundation, Tampere, Finland.

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The Authors

M. Talja, MD, Registrar in Urology, Helsinki University Central Hospital.

L. C. Andersson, MD, Professor of Pathology, University of Helsinki.

M. Ruutu, MD, Research Fellow, Helsinki University Central Hospital.

O. Alfthan, MD, Associate Professor in Urology, Helsinki University Central Hospital.

Requests for reprints to: M. Talja, Second Department of Surgery/Urological Unit, Meilahti Hospital, Haartmaninkatu 4, SF-00290 Helsinki 28, Finland.

British Journal of Urology (1985), **57**, 585-596

Case Reports

Cystitis Emphysematosa

JENNIFER M. ROCCA and J. McCLURE, *Division of Tissue Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia*

Cystitis emphysematosa is an inflammatory condition associated with gas-filled vesicles in the wall of the urinary bladder. Over 118 cases of the disease have been reported in the literature and about 50% were diabetics. The gas is probably a mixture of carbon dioxide and hydrogen produced by bacterial fermentation. The clinical features of cystitis emphysematosa have been delineated by Bailey (1961).

Case Report

A 75-year-old man who had been a diabetic for 18 years died as the result of a myocardial infarct. An incidental finding at necropsy was the presence of numerous gas-filled vesicles in the wall of the urinary bladder. These ranged from 1 to 10 mm in diameter and were particularly concentrated in the mucosa. Microscopically the vesicles (Fig. 1) were sometimes lined by flattened fibrocytes derived from the mucosal stroma, and multinucleated giant cells were also noted both in relationship to the wall of vesicles and free in the stroma. This also contained very small rounded spaces around which multinucleated giant cells were stretched (Fig. 2).

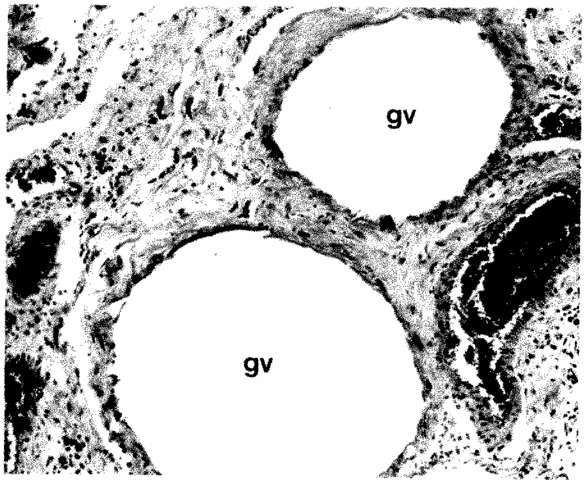

Fig. 1 Gas-filled vesicles (gv) in mucosa of urinary bladder. (H and E × 100).

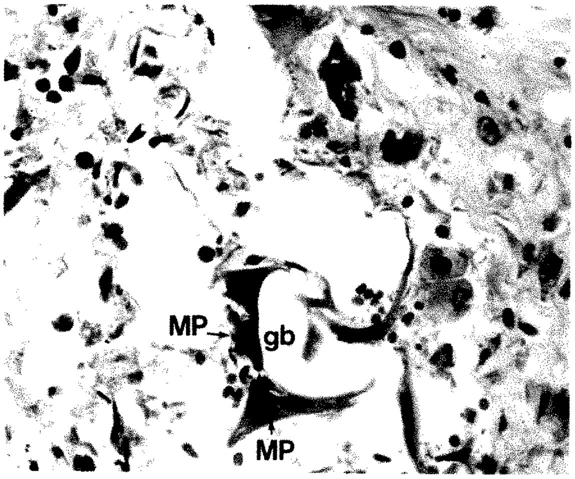

Fig. 2 Macrophage polykaryons (MP) stretched around small gas bubbles (gb). (H and E × 400).

Comment

The presence of multinucleated giant cells in various forms of cystitis has been discussed by Wells (1938). In the present case these cells had the histological features of macrophage polykaryons. Their attenuated relationship to small, presumably gas-filled spaces suggests that they may be forming by the fusion of macrophages attempting simultaneously to phagocytose small bubbles of gas by the mechanism suggested by Chambers (1977). This further suggests that cystitis emphysematosa is an *ante mortem* phenomenon.

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Carcinoma of the Prostate Presenting with Massive Pleural Effusion and Elevated Pleural Acid Phosphatase

M. J. D. CASSIDY, G. R. KEETON and P. A. BERMAN, *Department of Medicine, University of Cape Town Medical School and Somerset Hospital, Cape Town, South Africa*

Carcinoma of the prostate presenting with pulmonary metastases is uncommon (Legge *et al.*, 1971), the usual pattern being that of lymphangitis carcinomatosa which may be accompanied by small pleural effusions. One pleural effusion of moderate size was reported by Scheidemandel *et al.* in 1972. We report a massive pleural effusion secondary to carcinoma of the prostate in which the pleural fluid prostatic acid phosphatase was markedly elevated in the face of a normal serum acid phosphatase.

Case Report

A 67-year-old man presented with a 1-week history of increasing dyspnoea and right-sided pleuritic chest pain. He complained of difficulty in initiating micturition over the previous year, terminal dribbling and he had lost 20 lb in weight. He was severely dyspnoeic at rest and centrally cyanosed. The heart rate was 140 beats/min and blood pressure 120/89 mm Hg. A massive right-sided pleural effusion was confirmed on chest X-ray and rectal examination revealed a hard craggy prostate. Total serum acid phosphatase was 0.5 Bessey Lowry Brock (BLB) units/l (normal 0.15-0.7 BLB units/l); tartrate labile acid phosphatase 0.15 BLB units/l (normal 0.01-0.3 BLB units/l); total pleural fluid acid phosphatase 3.5 BLB units/l and tartrate labile pleural fluid acid phosphate 1.58 BLB units/l. Column chromatography of the enzymes showed over 70% to be prostatic (Fig.). Clusters of adenocarcinoma cells were seen on cytological examination and histological examination of a pleural biopsy showed small atypical cells arranged in acinar formation. A prostatic needle biopsy showed a well differentiated adenocarcinoma and a technetium bone scan showed multiple secondary deposits. Despite 4 litres of fluid aspirated, rapid reaccumulation occurred together with recurrent dyspnoea. Treatment with stilboestrol 5 mg, reducing to 1 mg 8-hourly after 48 h, resulted in complete resolution of the effusion.

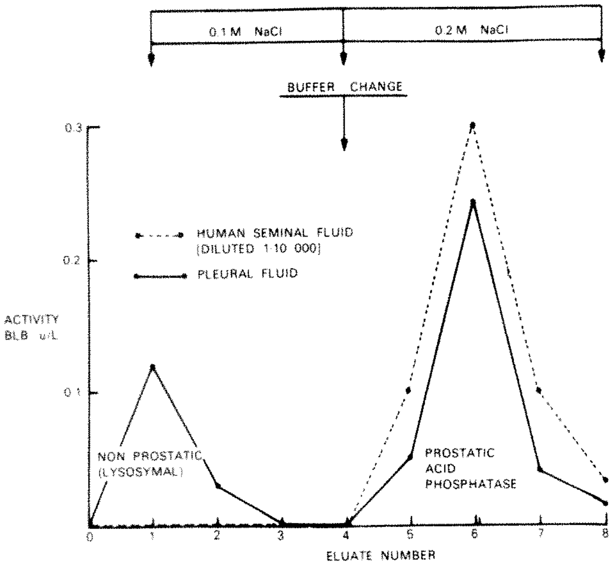

Fig. DEAE Sephadex chromatography of pleural aspirate run in parallel to human seminal fluid to demonstrate identity of second peak to human prostatic acid phosphatase.

Comment

Although the pleural effusion was thought to be due to metastatic deposits from the prostatic primary, a normal serum acid phosphatase was misleading. The elevated pleural fluid acid phosphatase, however, suggested the prostatic origin of the neoplasm. This resulted in early institution of therapy before the results of histology were available. An elevated acid phosphatase could, however, reflect a non-specific lysozyme release from cell damage in a malignant process. Column chromatography was performed which separated the non-specific lysozymal enzyme from the prostatic isoenzyme which was dominant (Fig.)

Measurements of acid phosphatase in pleural effusions of multiple aetiologies have shown that it is likely that only pleural metastases due to carcinoma of the prostate will have elevated levels of pleural fluid phosphatase (Veran *et al.*, 1965). Presentation with critical dyspnoea due to massive pleural effusion, secondary to carcinoma of the prostate, has not to our knowledge been described. The patient's response to stilboestrol was similar to that of two previously reported cases of carcinoma of the prostate with pleural and pericardial effusions.

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Requests for reprints to: M. J. D. Cassidy, Renal Unit, Groote Schuur Hospital, Observatory, Cape Town, South Africa.

Malignant Lymphoma of the Ureter

R. J. LIGTHELM and T. A. LISTER, *Imperial Cancer Research Fund Department of Medical Oncology, St Bartholomew's Hospital, London*

Two cases of malignant lymphoma with ureteric involvement are reported.

Case Reports

Case 1 A 60-year-old man presented with renal colic. Retrograde ureterography showed marked narrowing of the distal ureter with dilatation above the level of L5-S1.

At laparotomy a woody, indurated tumour was found surrounding the right ureter. Histological examination revealed a malignant lymphoma (Kiel: mixed diffuse and follicular centroblastic-centrocytic).

Lymphangiography showed possible involvement of the para-aortic nodes; bone marrow biopsy was normal.

Case 2 A 71-year-old man presented with severe anaemia and uraemia. High dose IVU showed left renal enlargement with late and faint opacification of dilated calices; retrograde ureterography revealed left ureteric obstruction by a non-opaque mass.

At laparotomy a mass was found surrounding the left ureter and the left kidney was grossly abnormal. Enlarged external iliac nodes were found. Renal histological examination showed ischaemic changes, chronic pyelonephritis and areas of hyalinisation. Retroperitoneal biopsies showed fibrosis, amyloid and clumps of malignant lymphocytes. Lymph node and bone marrow biopsy confirmed malignant lymphoma (Kiel: lymphoplasmacytoid).

Comment

There are only two previously reported cases of patients with malignant lymphoma presenting with urological symptoms (Couto *et al.*, 1965; Goswami, 1977), although asymptomatic uretero-peritoneal involvement is well recognised (Lucke and Schulmberg, 1957; Givler, 1971; Sufrin *et al.*, 1977).

In view of the relatively high incidence of microscopic ureteric involvement found by Givler (1971), it is surprising that more asymptomatic cases have not been reported. The likely explanation of this is that it passes undiagnosed in the face of other problems encountered at presentation with disseminated lymphoma.

Acknowledgements

We thank Mr J. E. A. Wickham and Mr W. F. Hendry, Department of Urology, St Bartholomew's Hospital, for referring the patients and Dr A. G. Stansfeld for making the diagnosis.

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Requests for reprints to: T. A. Lister, ICRF Department of Medical Oncology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Successful Reconstruction Following Circumcision with Diathermy

A. AZMY, S. A. BODDY and P. G. RANSLEY, *Department of Urology, Hospital for Sick Children, London*

Case Report

B.B. was referred at the age of 3 years, having been circumcised as a neonate, using diathermy. He had developed extensive burns of the coronal sulcus and distal part of the shaft of the penis, which left the glans almost completely severed from the corpora. Examination showed that the glans was viable and connected to the corpora by a stalk 2 mm in diameter (Fig. 1). The glandular urethra was intact but he voided through a hypospadiac opening on the termination of the truncated shaft. Operative correction was undertaken in a single stage.

Under a tourniquet, the base of the glans penis, the surface of the vascular pedicle and the distal portion of the shaft were denuded of skin and epithelium. The glans was further cut back to expose true glandular tissue.

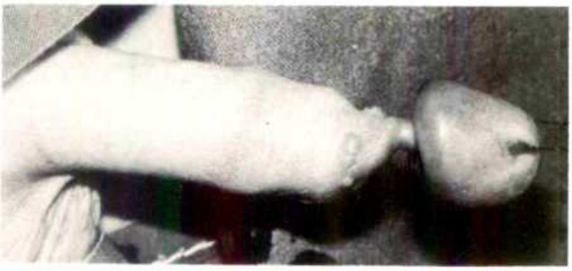

Fig. 1 The connection of the glans to the corpora with a fine stalk is shown.

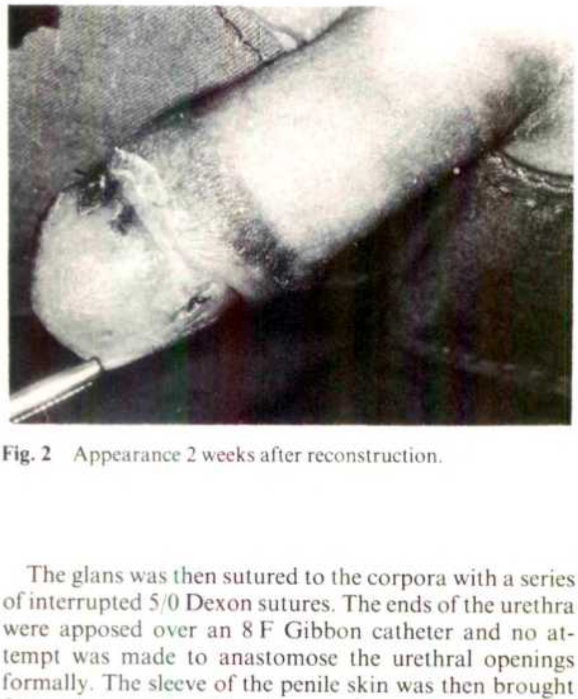

Fig. 2 Appearance 2 weeks after reconstruction.

The glans was then sutured to the corpora with a series of interrupted 5/0 Dexon sutures. The ends of the urethra were apposed over an 8 F Gibbon catheter and no attempt was made to anastomose the urethral openings formally. The sleeve of the penile skin was then brought forward and sutured to the margins of the glans. The catheter remained *in situ* for 2 weeks. Recovery was uneventful and a satisfactory appearance resulted (Fig. 2), the patient voiding normally and without difficulty from the terminal urethral opening.

Comment

Circumcision should not be regarded as a minor operation. It requires a careful, unhurried technique, good general anaesthesia and an assistant (Johnston, 1978).

Circumcision is not devoid of complications. Post-operative haemorrhage may occur, partial (or even complete) amputation is not unknown and extensive burning of the glans with sloughing of the penis may follow the use of diathermy (Eckstein, 1972).

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Requests for reprints to: A. Azmy, Department of Paediatric Urology, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

Fibrosarcoma of the Penis: Recurrence 7 Years after Local Excision

G. RENDERS and C. CUVELIER, *Departments of Urology and Pathology, University Hospital, Ghent, Belgium*

Case Report

A 56-year-old male first noticed a swelling on the dorsum of his penis in 1969 but did not seek medical advice until 1973. He was found to have a small painless nodule of the foreskin. All clinical and laboratory findings were normal and circumcision was performed. Histopathological examination revealed well differentiated fibrosarcoma. After a few months the patient was lost to follow-up. In May 1980 he presented with a painless induration of the dorsum of the penis. The induration was superficial and proximal to the coronal sulcus. There was no regional lymphadenopathy and all investigations were normal. The tumour was widely excised and proved to be a disc 2 cm in diameter, completely free of the corpora cavernosa. Microscopic examination showed well differentiated fibrosarcoma (Fig.).

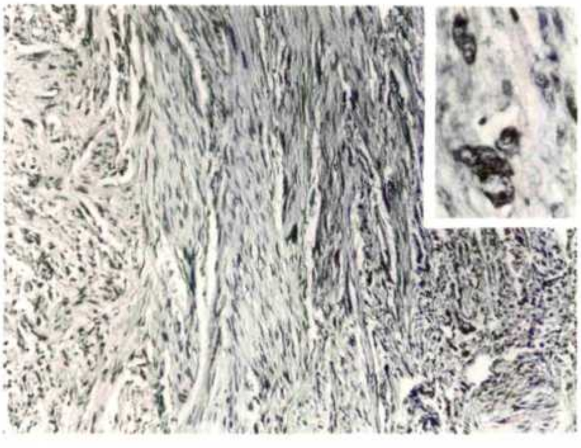

Fig. Interlacing bundles of well differentiated fibroblastic cells surrounded by abundant connective tissue. Mitoses are frequent and nuclear pleomorphism is obvious. (H and E ×78; inset ×314).

Comment

Sarcoma of the penis is rare and according to McKenzie Pratt and Ross (1969) its site of origin determines treatment and clinical behaviour. The tumours which present as small nodules in the superficial tissues of the shaft of the penis arise from the subcutaneous tissues, are of low malignancy and show little tendency to invade the deeper structures. Treatment is wide local excision. A second group of tumours arise from the corpora and are situated more deeply, though histologically they are identical to the first group. They tend to invade the corpora locally, with high risk of early metastases. Treatment is radical amputation of the penis.

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Requests for reprints to: G. Renders, Department of Urology, University Hospital, De Pintelaan 135, B-9000 Ghent, Belgium.

Ultrasonic Detection of Urethral Calculus

J. GAMMELGAARD and S. M. HASTAK, *Department of Urology H, Herlev Hospital, Copenhagen, Denmark*

Urethral calculi form a small percentage of urinary tract calculi. The presenting features are sometimes very characteristic but complex, *e.g.* perineal pain, dysuria, haematuria or weak stream. The atypical cases, however, may pose a diagnostic problem.

Case Report

A 63-year-old male was admitted with sudden onset of urinary retention. Past history revealed one attack of right ureteric colic 5 years previously followed by spontaneous passage of a stone.

On admission the bladder was distended 2 cm below the umbilicus. Rectal palpation revealed an enlarged prostate of about 50 g. Catheterisation *per urethram* failed despite several attempts and a false passage was suspected. The bladder was drained by suprapubic catheter and transurethral resection of the prostate was planned.

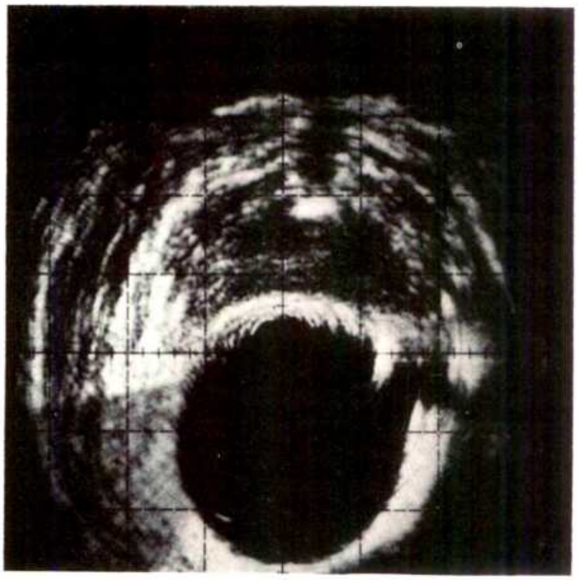

Fig. 1 Transrectal ultrasonic scan of the prostate. Arrow shows the echodense area of a calculus with shadowing.

Transrectal ultrasonic scanning was performed for pre-operative estimation of prostatic volume. The scan showed an echodense area with shadowing behind situated anteriorly in the midline (Fig. 1). Subsequent urethrography confirmed the ultrasonic suspicion of a calculus in the prostatic urethra and the clinical suspicion of a false passage (Fig. 2). A stone measuring 0.5 × 1 cm was removed transurethrally. Post-operative follow-up 15 days later showed maximum flow rate of 22 ml/s.

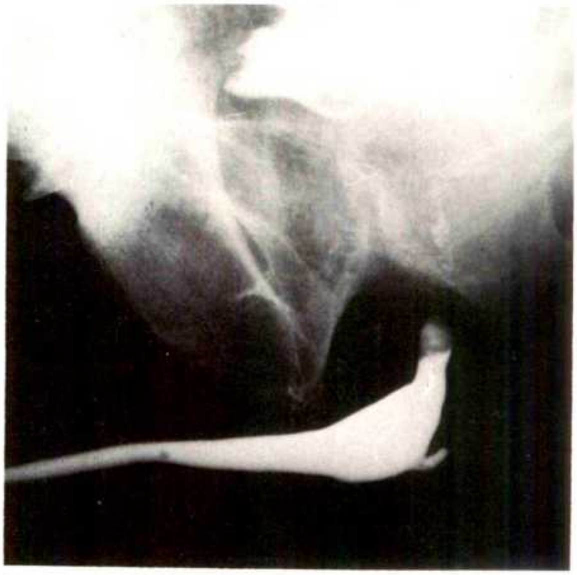

Fig. 2 Retrograde urethrography. Thick arrow shows the calculus in the urethra. The false passage is indicated by a thin arrow.

Comment

The present case was misleading because of the absence of classical features in the history, the age of the patient and the findings on rectal palpation.

Plain X-ray and IVU fail to demonstrate urethral calculi in most cases (Paulk *et al.*, 1976).

Transrectal ultrasonography, which is a non-invasive procedure, usually demonstrates stones in the prostatic region and is a valuable alternative in diagnosing urethral calculi.

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Requests for reprints to: J. Gammelgaard, Ultrasonic Laboratory 54 H1, Department of Urology H, Herlev Hospital, DK2730 Herlev, Denmark.

Acute Renal Failure Secondary to Fishing Line

R. J. L. WILLIAMS, A. FREEMAN and C. B. BRENDLER,
Departments of Urology and Renal Medicine, Royal Infirmary, Cardiff

Case Report

A 22-year-old man was admitted in acute renal failure requiring dialysis. Ten years previously he had twice inserted a length of nylon fishing line into his urethra and was unable to retrieve the end on the second occasion. For the past 5 years he had had continuous suprapubic pain and intermittent difficulty in passing urine.

Plain X-rays showed a large calculus filling the bladder with a smaller stone intermittently prolapsing into the prostatic urethra (Fig. 1). IVU showed severe bilateral hydronephrosis with marked loss of renal cortex. Following removal of the stones his renal function returned to normal and the stones were found to be connected by the fishing line (Fig. 2).

Comment

Stone formation on foreign bodies in the bladder has been widely reported, the usual underlying causes being either iatrogenic or self-introduced (Frozanpour, 1976). Self-introduction almost always has a sexual motivation (Bichler, 1971) and there is usually delay in seeking medical attention as a result of shame and guilt. Massive bladder stones (Williams *et al.*, 1977) often cause remarkably few symptoms since they have no room to move and may or may not cause upper tract damage. However, in this instance the patient's intermittent difficulty with micturition and subsequent renal failure related to intermittent prolapse of the smaller stone into the prostatic fossa.

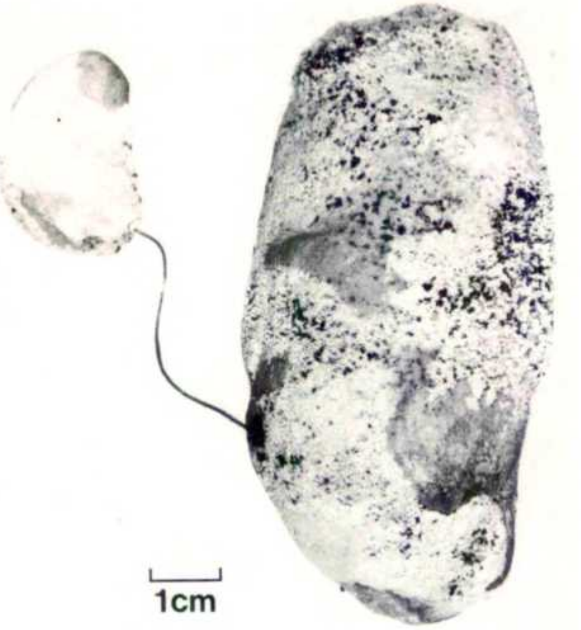

Fig. 1

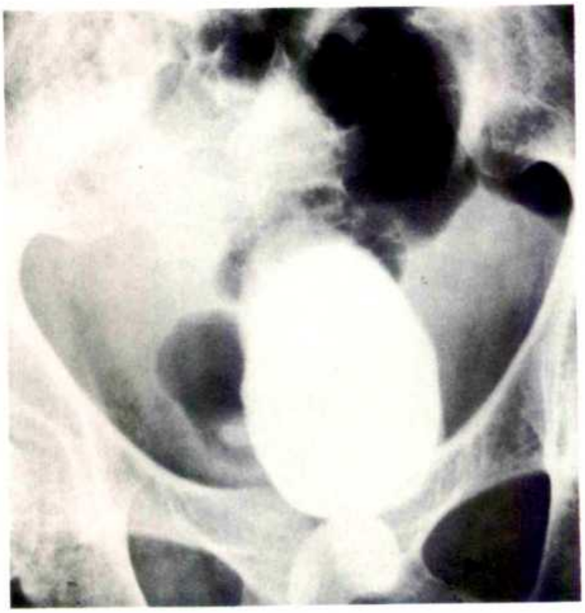

Fig. 2

Acknowledgements

We thank Mr T. P. Stephenson and Dr G. A. Coles for allowing us to report this case.

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Requests for reprints to: R. J. L. Williams, Registrar in General Surgery, St Mary's Hospital, Praed Street, London W2 1NY.

Carcinoid Tumour of the Prostate Associated with Inappropriate ACTH Secretion

D. SLATER, *Department of Histopathology, Royal Hallamshire Hospital, Sheffield*

Case Report

A 69-year-old man presented with oliguria, haematuria and nocturia. A hard irregular prostate gland was found on rectal examination. There was no clinical evidence of either Cushing's or the carcinoid syndrome, and the skin was not pigmented. An intravenous urogram demonstrated right hydronephrosis with a prostatic filling defect in the bladder. The plasma urea was 20 mmol/l; potassium 2.2 mmol/l; bicarbonate 40 mmol/l; acid phosphatase 0.5 iu/l; blood sugar 20 mmol/l. The urinary potassium was 46 mmol/l. Treatment was commenced with potassium supplements and subcutaneous insulin. Shortly after admission a right perinephric abscess required surgical drainage but, despite antibiotic treatment, death occurred from a *Pseudomonas* septicaemia. Biochemical investigations showed a plasma cortisol at 9.00 am and 11.00 pm of over 1200 mmol/l; serum C-terminal ACTH 340 pg/ml; urinary 17-oxogenic steroids 211 μmol/24 h; urinary 17-oxosteroids 166 μmol/24 h; urinary free cortisol 1600 nmol/24 h. No suppression of plasma cortisol or ACTH levels was observed over 3 days with 8 mg dexamethasone daily.

Autopsy demonstrated a tumour completely replacing the prostate gland with extension into the base of the bladder and around the right ureteric orifice. There was no evidence of spread to other organs. Histological examination revealed a neoplasm composed of small, spindle-shaped cells with a perivascular, packeted configuration (Fig.). Special stains showed argyrophil-positive granules within the tumour cells and electron microscopy demonstrated that the granules were electron-dense, membrane-bound and had a diameter of approximately 140 nm. These appearances were considered to be those of a primary carcinoid tumour of the prostate. Histological examination of the adrenal cortex showed bilateral hyperplasia and was of the type associated with stimulation by inappropriate ACTH. Biochemical investigations on the tumour showed a C-terminal ACTH concentration of 20 μg/g wet tissue.

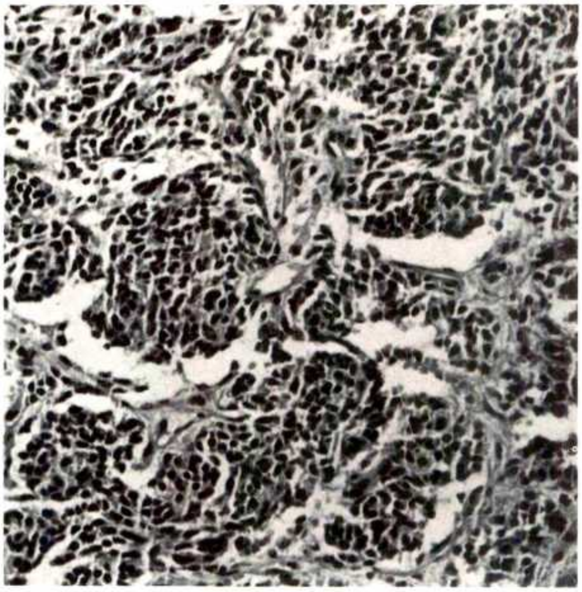

Fig. Carcinoid tumour cells (H and E × 45).

Comment

Argentaffin and argyrophil cells have been demonstrated in normal prostatic tissue (Kazzaz, 1974). They are present in a minority of prostatic neoplasms (Kazzaz, 1974) and two cases of prostatic carcinoma have been described in which areas of carcinoid tumour were also present (Azzopardi and Evans, 1971). Hypokalaemic alkalosis due to the inappropriate secretion and ACTH has previously been associated with prostatic carcinoma (Azzopardi and Williams, 1968). However, this appears to be the first report of a pure prostatic carcinoid tumour associated with inappropriate ACTH secretion.

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Requests for reprints to: D. N. Slater, Department of Pathology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX.

Renal Arteriovenous Fistula Following Nephrectomy

S. L. FELDMAN, D. PRESMAN and G. L. KANDEL, *Department of Urology, Michael Reese Hospital and Medical Center, Chicago, USA*

Case Report

A 16-year-old male was hospitalised with haematuria, fever and right flank pain. Intravenous urography revealed distortion of the right pelvicaliceal collecting system. Renal arteriography revealed stretched vessels without definite neovascularity. Nephrectomy was performed and the pedicle ligated *en masse* with 2/0 silk. A histological diagnosis of renal carcinoma was made. Persistent drainage from the right flank developed and a sinogram demonstrated a tract to the nephrectomy bed. Curettage of the tract revealed chronic inflammation. Eleven months post-operatively the patient presented with left flank pain. Examination revealed a bruit over the right flank. Renal arteriography demonstrated an arteriovenous fistula at the nephrectomy site (Fig.). A midline abdominal incision was made and the right renal artery and vein were ligated separately. The patient was discharged 10 days later.

Comment

Post-nephrectomy arteriovenous fistulas are extremely uncommon. They are thought to develop secondary to mass ligation of the renal pedicle, infection or renal carcinoma. Symptoms include a bruit over the nephrectomy incision in 90% of the cases, cardiomegaly in 80%, high output heart failure in 50% and pain in 40% (Maldonado *et al.*, 1964). The definitive diagnosis is made by renal arteriography. Treatment consists of surgical excision of the fistulous tract. Complete dissection of the fistula is warranted to ensure no evidence of collateral vessels (Goldstein *et al.*, 1967).

This patient's fistula was probably due to an inflammatory process but *en masse* ligation of the pedicle or residual tumour cannot be excluded.

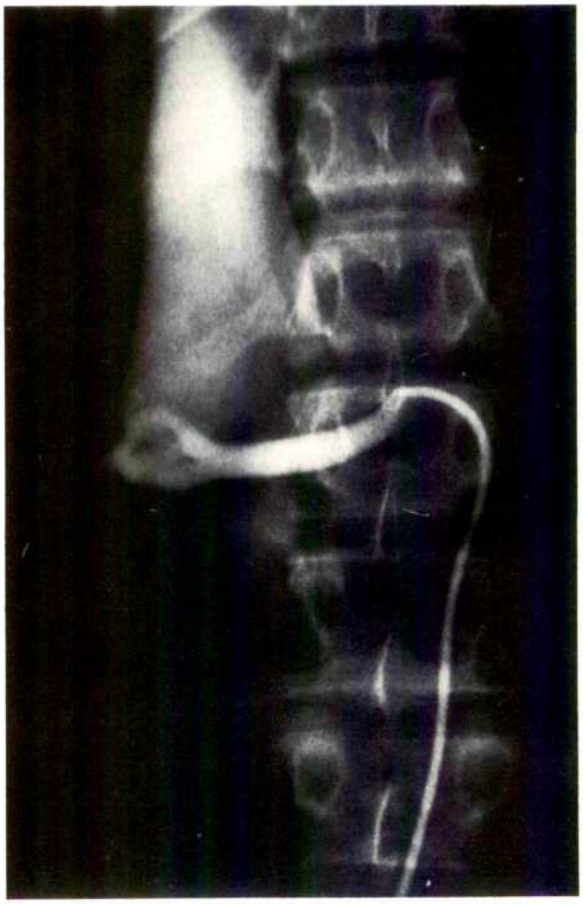

Fig.

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Goldstein, A. G., Delaurentis, D. A. and Schwartz, A. J. (1967). Post-nephrectomy arteriovenous fistula. *Journal of Urology*, **98**, 44-47.

Maldonado, J. E., Sheps, S. G., Bernatz, P. E., DeWeerd, J. H. and Harrison, E. G., Jr. (1964). Renal arteriovenous fistula. A reverisble cause of hypertension and heart failure. *American Journal of Medicine*, **37**, 499-513.

Requests for reprints to: S. L. Feldman, Department of Urology, Michael Reese Hospital and Medical Center, 29th Street and Ellis Avenue, Chicago, Illinois 60616, USA.

Primary Melanoma of the Urinary Bladder Presenting with Intracerebral Metastases

J. W. IRONSIDE and W. R. TIMPERLEY, *Department of Neuropathology, Royal Hallamshire Hospital, Sheffield*; J. W. MADDEN, *Department of Neurology, Royal Hallamshire Hospital*; J. A. ROYDS and C. B. TAYLOR, *Department of Biochemistry, University of Sheffield*

The urinary bladder is an extremely uncommon primary site for malignant melanoma. We report a patient who presented with metastatic intracerebral melanoma from an occult primary in the bladder.

Case Report

A 56-year-old man presented with a 5-week history of clumsiness of the left leg, intermittent left-sided headache and left facial weakness. A CT scan showed numerous hypodense nodules throughout the brain, biopsy of which showed the appearances of an amelanotic melanoma. Repeated clinical examination found no primary lesion in the skin or eyes. The patient received whole brain irradiation (300 cGy in 9 fractions over 2 weeks). He made an initial improvement, then gradually deteriorated until his death 8 months later.

Post mortem examination showed numerous deposits of metastatic melanoma in the brain. The bladder mucosa bore a nodular non-pigmented tumour, 7 mm in diameter (Fig. 1), with the histological and untrastructural features of a malignant melanoma. Immunocytochemistry demonstrated γ enolase and S100 protein in the bladder and brain lesions (Fig. 2). No other metastases were identified and careful examination of the skin and internal organs showed no other possible primary neoplasm.

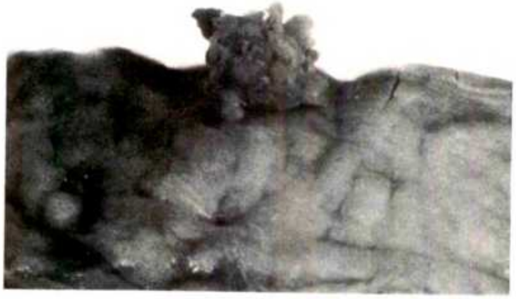

Fig. 1 The primary lesion in the bladder is a partly necrotic nodule (× 2).

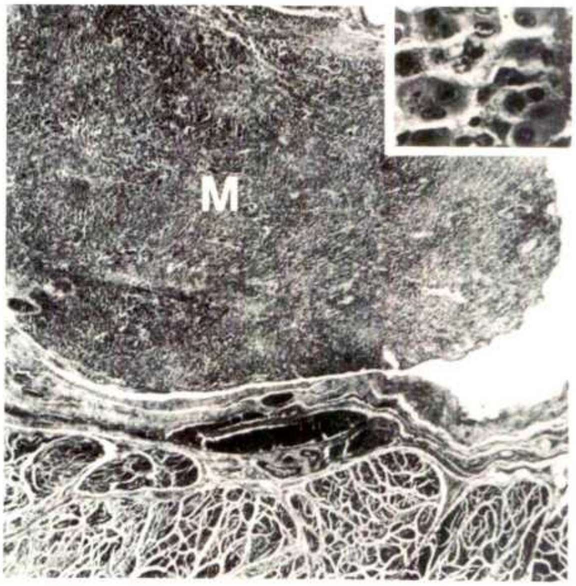

Fig. 2 The melanoma (M) is invading the submucosa and encroaching on blood vessels (H and E × 80). Inset: Gamma enolase is present within the cytoplasm of the melanoma cells (Peroxidase-antiperoxidase × 700).

Comment

Only four previous cases of malignant melanoma arising in the urinary bladder have been reported (Ainsworth *et al.*, 1974; Willis *et al.*, 1980; Anichkov and Nikonov, 1982); in these cases the diagnosis was made on histological and ultrastructural studies alone. S100 protein and γ enolase are immunocytochemical markers for melanoma and have not previously been demonstrated in neoplasms arising in the bladder. In contrast to the previous cases, no evidence of haematuria was found in our patient and no other urinary signs or symptoms were present. Examination of the lower urinary tract may prove valuable in future patients with metastatic melanoma when a primary neoplasm cannot be identified elsewhere.

Acknowledgements

We are grateful to Miss P. Little for technical assistance. Dr J. A. Royds is supported by the Wellcome Trust (Grant No. 11353/1.5).

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Requests for reprints to: J. W. Ironside, Department of Neuropathology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

Points of Technique

Entangled Urinary Catheters—Prevention of a "Knotty" Problem

J. A. THORNHILL, *Mayday Hospital, Thornton Heath, Surrey CR4 7YE*

Percutaneous suprapubic bladder drainage via an indwelling catheter is frequently used to relieve acute urinary retention in cases where catheterisation *per urethram* has failed. It is common practice following any subsequent operative procedure, such as division of a stricture or transurethral prostatectomy, to insert a urethral catheter and remove the suprapubic drainage system.

In a recent case treated by the author, a flexible narrow bore suprapubic catheter, initially inserted in the above acute circumstances, later became entangled with a urethral catheter which was inserted immediately after an operation to relieve a urethral stricture. Such entanglement prevented the removal of the suprapubic catheter. With difficulty, both catheters were withdrawn *en bloc* via the urethra (Fig.), and this probably contributed to post -operative peri-urethritis.

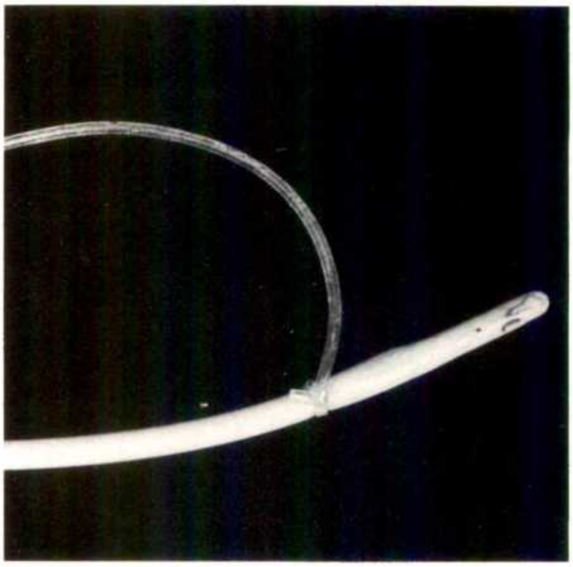

Fig. The entangled urethral and suprapubic catheters following removal *en bloc* via the urethra.

The entanglement of catheters in these circumstances must be very rare, although other complications with similar suprapubic catheters have been described (Drutz and Khosio, 1984). To prevent a recurrence, two possible technical options are available. Firstly, removal of the suprapubic pigtail catheter before insertion of the urethral catheter obviously precludes their entanglement, although it cannot prevent knotting of the suprapubic catheter alone. Secondly, a firm wider bore balloon type suprapubic catheter, several commercial brands of which are available, is recommended, since its inherent design should prevent any entanglement. The latter proposal is more logical, as it is unwise to remove any suprapubic catheter until distal drainage has been proven free of obstruction; in the case described above a urethral stricture required local treatment.

It seems prudent to use the firmer wide bore balloon type suprapubic catheter rather than the narrow bore pigtail design in the emergency management of acute retention when it is not possible to pass a urethral catheter.

Reference

Drutz, H. P. and Khosio, H. I. (1984). Complications with Bonano suprapubic catheters. *American Journal of Obstetrics and Gynecology*, **149**, 685-686.

Requests for reprints to: J. A. Thornhill, 110 Ashley Rise, Portmarnock, Co. Dublin, Irish Republic.

Steerable Guide-Wire for Insertion of Ureteric Stent into Tortuous Ureter

N. T. SCHMELLER and H. OVERBECK, *Department of Urology, Medizinische Hochschule, Lübeck, West Germany*

Temporary insertion of a ureteric stent may sometimes be necessary in patients with either prostatic or bladder tumours where there is stenosis at the vesicoureteric junction and a wide and tortuous ureter above.

A relatively stiff ureteric catheter or stent is needed to penetrate the stenosis in the distal ureter but a pliable tip is required to follow the tortuous course of the ureter into the pelvis. To solve this problem we have used a guide-wire (Angiomed, Ettlingen, West Germany) in which the tip flexibility is steerable from outside. The guide-wire is inserted through the stenosis with the stiff tip. Thereafter, by pulling back the inner stiff part of the guide-wire, the tip can be made flexible and as long as desired. The memory effect of the renal pelvis pigtail of the ureteric stent will now bend the tip of the stent and thus even extreme curves of the ureter may be negotiated. The stent may be straightened by advancing the stiff inner portion of the guide-wire.

Requests for reprints to: N. Schmeller, Klinik für Urologie, Medizinische Hochschule Lübeck Ratzeburger Allee 160, 2400 Lübeck, West Germany.

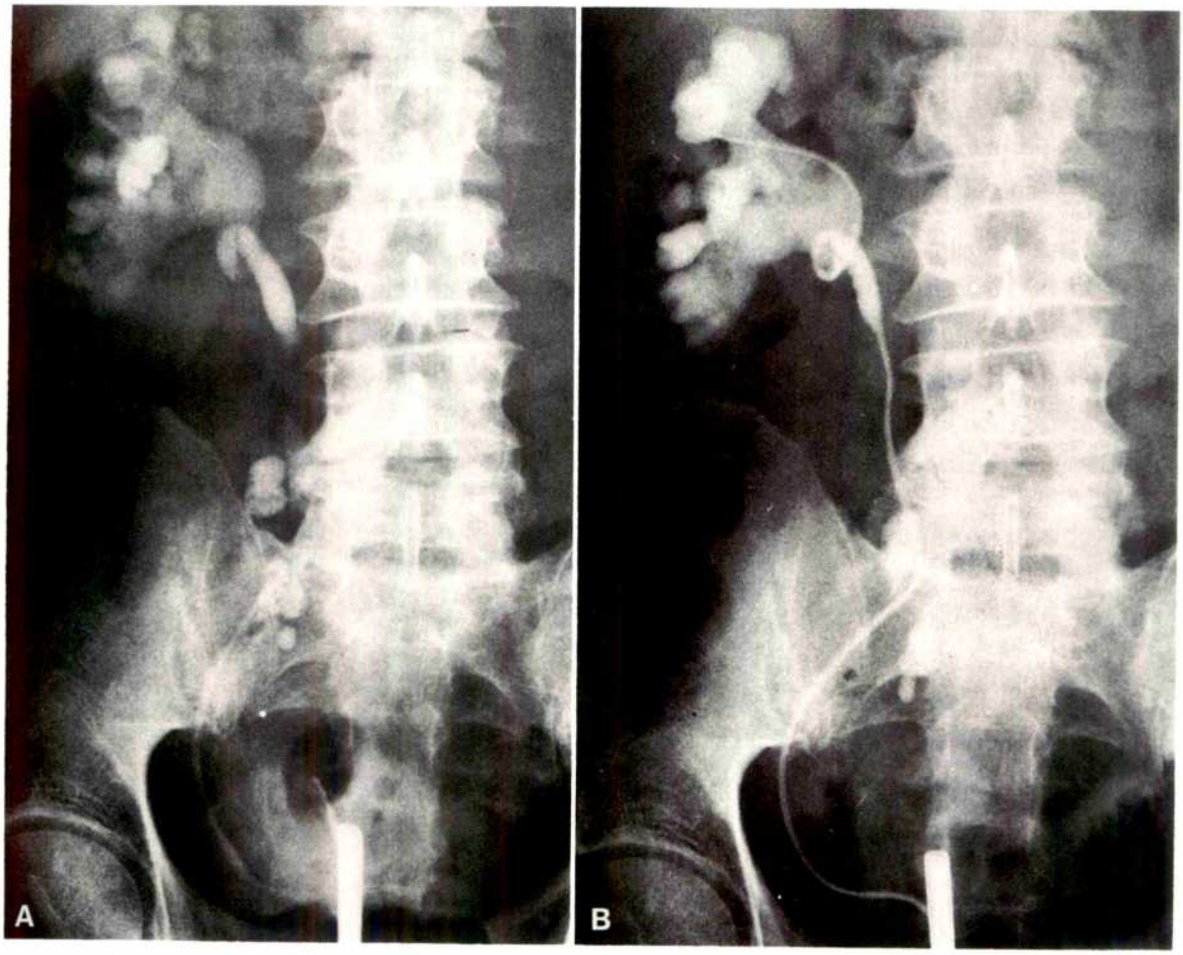

Fig. (A) Tortuous ureter in a patient with ureteric stenosis. (B) Insertion of ureteric stent with steerable guide-wire.

A New Technique to Reconstruct the Glans Penis in a Patient with a Buschke-Loewenstein Tumour

H. COSTA, P. SANTOS, R. SOARES and J. AMARANTE,
Department of Plastic and Reconstructive Surgery, Hospital Escolar de S João, Oporto, Portugal

After distal amputation of the penis because of a Buschke-Loewenstein tumour, a new glans was made by covering the stump with a skin graft and recreating a new foreskin with part of the remaining penile skin.

After distal amputation of the penis 2 cm proximal to the lesion (Fig. 1A), the corpora cavernosa and the corpus spongiosum were sutured together (Fig. 1B), creating a semi-spherical stump with the urethral opening at its centre. The stump was covered with a split thickness skin graft (Fig. 2A). The remaining skin of the penis was reflected and sutured to the edge of this skin graft, creating a new coronal sulcus and foreskin (Fig. 2B).

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Requests for reprints to: J. Amarante, Servico de Cirurgia Plástica, Hospital Escolar de S João, 4.200 Oporto, Portugal.

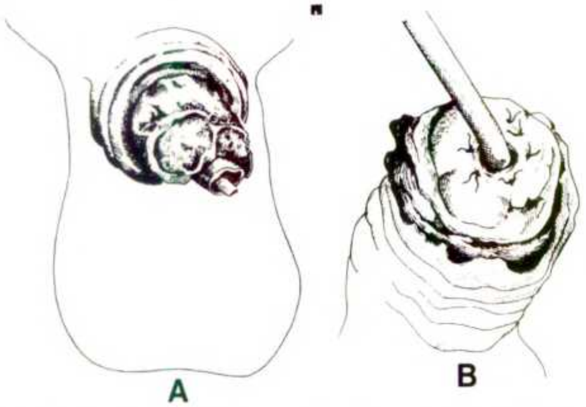

Fig. 1(A) The stump of the penis after amputation. (B) The semi-spherical new glans with the urethral opening at the centre.

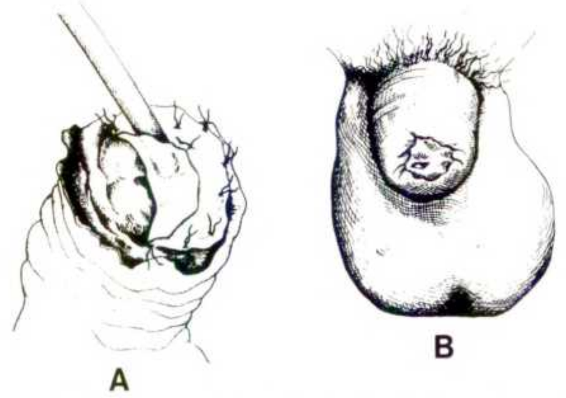

Fig. 2(A) The new glans with the split thickness skin graft being sutured. (B) The final result.

British Journal of Urology (1985), **57**, 597-598

Notices

Institute of Urology (University of London) in association with St Peter's Hospitals

Outline Programme of Courses and Seminars

6-7 December 1985	Uro-Radiology Weekend
13-14 December 1985	Controversies in Urology
Spring or Summer 1986	Seventh Practical Course on Percutaneous Renal Surgery and Radiology
16-17 June 1986	Reconstructive Urology

Further particulars from; Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01 240 9115.

Urological Research Meeting

Guy's Hospital, London. 10 January 1986

The meeting will provide a forum for the informal presentation and discussion of completed work and work in progress with invited participants from the related basic sciences such as smooth muscle physiology and pharmacology, oncology, anatomy and nephrology.

Further particulars from: Mr A. R. Mundy, Department of Urology, Guy's Hospital Medical School, London Bridge, London SE1 9RT. Please state if you wish to present a paper.

British Association of Urological Surgeons and Canadian Urological Association

Presidents: Professor J. P. Blandy, MA, DM, MCh, FRCS, FACS; Dr G. A. Farrow, MD, FRCS(C), FACS

Annual Meeting: London, 17-20 June 1986

The 1986 meeting will be held in conjunction with the Canadian Urological Association and will therefore have an expanded scientific programme commencing on Tuesday morning, 17 June 1986. Abstracts of papers, posters and videotapes to be considered by the Programme Sub-committee should be submitted to the Honorary Secretary by Friday, 10 January 1986. Abstracts should be submitted on the special forms available from the BAUS Secretariat and must have a clear statement as to whether the submission is a paper, a poster or a video. Abstracts submitted in any other form will not be considered.

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Bard Silver Medal Award

The award, which will consist of the sum of £1500 and the Bard Silver Medal, will be given at the Annual Meeting of the Association to be held in London in 1986. The award is given for the best essay submitted specifically for consideration for the award by members of the Association and a paper, based on the successful essay and not exceeding 30 minutes' duration, will be given at a specified time in the programme of the meeting. The presentation of the Award will then be made by the President.

The adjudication of essays will take place in March 1986 and the adjudicators will be Professor N. J. Blacklock, the President, the Vice-President, the immediate Past President and the Honorary Secretary of the Association. To ensure that the award is presented for papers of the highest quality only, the Committee may decide that no award be made in any one year.

Essays for consideration for the award should not exceed 35,000 words and six typewritten copies are requested. They should be submitted not later than 1 March 1986 to: The Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

DANTEC Urology Prize

An annual prize (formerly known as the DISA Urology Prize) will be awarded by DANTEC for the best scientific paper contributing towards the understanding of urinary tract function which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will consist of a travel voucher for £400.00 and a token presentation gift. The winner will be notified before the BAUS Annual Meeting and the prize will be presented at the meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to: The Honorary Secretary, The British Association of Urological Surgeons at The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN.

12th Meeting of the International Study Group for Steroid Hormones

Rome, Italy. December 1985

The main topics of the meeting will be:

1. Steroid peptide interaction
2. Sex hormone antagonists.
3. Intratissular steroids and hormone dependent corneu.

Deadline for presentation of abstracts: 30th June 1985.
Further particulars from: Professor F. Sciarra, V Clinica Medica, Università di Roma, viale del Policlinico, 00161 Rome, Italy.

Fifth International Symposium of Operative Andrology: Erection

Berlin, Germany. 15 March 1986

Further particulars from: A. Kelami, Department of Urology, Klinikum Steglitz, Free University of Berlin, Hindenburgdamm 30, D-1000 Berlin 45, F. R. Germany, or J. P. Pryor, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

Urological Society of Australasia. 39th Annual Scientific Meeting

Perth, Western Australia. 6–11 April 1986

Further particulars from: A. I. Low, 167 St George's Terrace, Perth 6000, Western Australia.

Sixth International Symposium on Radionuclides in Nephro-urology

Lausanne, Switzerland. 5-7 May 1986

Topics: Radionuclides and complementary/competitive methods in the investigation of kidneys, urinary tracts and relative bone disease. Basic and clinical sciences.

Deadline for submission of abstracts: 16 December 1985.

Further particulars from: A. Bischof-Delaloye, Division Autonome de Médecine Nucléaire, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland.

Seventh Congress of European Association of Urology

Berlin, Germany. 15 March 1986

Further particulars from: Professor F. Balogh, Department of Urology, Semmelweis University of Medicine, Maria U. 39, 1085 Budapest VIII, Hungary.

Second World Meeting on Impotence and Fifth Conference on Vasculogenic Impotence and Corpus Cavernosum Revascularisation

Prague, Czechoslovakia. 17-20 June 1986

Topics will include research on the physiology and haemodynamics of erection, morphological (angiographic) and functional examination of cavernous bodies of afferent and efferent vascular and neural pathways, and conservative and surgical treatment.

A pre-Congress teaching session will be held on 16 June 1986.

Further information from: V. Michal, Institute for Clinical and Experimental Medicine, Videnska 800, 146 22 Prague 4, Czechoslovakia.

Workshop on Testicular Tumours

Copenhagen, Denmark. 16–19 August 1986

The programme will include lectures and free communications on the following topics: morphology and function of the germ cell, cell lines, chromosome markers and oncogenes, histochemistry and monoclonal antibodies, carcinoma *in situ*, screening, prognostic factors, treatment, toxicity, and fertility.

Further information from: Dr M. Rørth, Department of Oncology II, Finsen Institute, 49 Strandboulevarden, DK-2100 Copenhagen, Denmark.

Fifth Congress of European Society for Urological Oncology and Endocrinology

Edinburgh, 18 and 19 August 1986

The programme will include plenary lectures by invited speakers, free communications and poster sessions on the following topics: oncogenes and growth factors, prostate receptors and metabolism, stromal/epithelial interactions, urological tumour markers, and hormone independent tumours and tumour resistance.

Further particulars from: F. K. Habib, Department of Surgery/Urology, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG.

British Journal of Urology (1985), **57**, 599-602

Book Reviews

The Pharmacology of the Urinary Tract. (Clinical Practice in Urology). Edited by M. Caine. Pp. xi + 167. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1984. Price DM 98.--; approx. £26.00.

This is another excellent book in the series "Clinical Practice in Urology". With an experienced editor such as Marco Caine it is not surprising that everything one needs to know about drugs and their action on the urinary tract is to be found in this book. However, the reviewer feels that the balance is not quite right. Part I consists of three chapters on the pharmacological action of drugs on the lower urinary tract and is a very clear account of current knowledge. The upper urinary tract has a chapter to itself: the pathophysiology of obstruction and disordered peristalsis are discussed and the wide variety of drugs that have been used and their management are mentioned. The chapters that follow on neuropathic and non-neurogenic bladder problems contain a great deal of duplicated information. Perhaps it would have been better to ignore this difference and discuss ways of altering bladder emptying, bladder storage and outlet activity regardless of aetiology. Many drug trials have been poorly controlled. Alan Wein does point out some of these deficiencies but a more critical review of the drugs used would have been helpful. Eighteen pages on the use of alpha-blockers in prostatic hypertrophy are probably excessive, while five pages on steroids in urology are inadequate.

Despite these criticisms the book is recommended for those who need to have a better understanding of the rationale of the use of drugs in urology.

Pathological Basis of Renal Disease. Second edition. By M. S. Dunnill. Pp. viii + 568. Eastbourne: Bailliere Tindall/Saunders. 1984. Price £29.50.

The first edition of this book appeared in 1976; now, 8 years later, it has been revised. In the process it has increased in length by 100 pages—largely due to the introduction of four chapters on renal tumours, renal stone, renal tubular disorders and cystic disease of the kidney. Despite this increase in length the book is virtually the same size and in fact weighs less than the first edition. This has been achieved by using smaller print and better quality paper. Apart from the early chapters, which include an update on current thinking on proteinuria, most of the original chapters are largely unchanged.

This book competes with Heptinstall, now a three-volume American tome, and also with a number of books on the subject of renal biopsies and glomerular disease in particular. Indeed there is a surplus of good books on what could be termed "medical renal pathology" but a striking scarcity of textbooks on urological pathology—dealing with surgical renal disease as well as diseases of the bladder, prostate and testis.

This is a good, readable textbook on renal pathology which by current standards is excellent value for money. Although pathologists, renal physicians and medical libraries will undoubtedly buy the book, the sale to urologists and departments of urology will probably be limited.

Wound Healing for Surgeons. Edited by T. E. Bucknall and H. Ellis. Pp. ix + 344. Eastbourne: Bailliere Tindall/Saunders. 1984. Price £19.75.

This book deals with general principles and then concentrates on wound healing in specific areas. The opening chapters provide a good scientific background on the pathology and biochemical changes involved in the healing of a wound. The bioengineering features of wound healing are then discussed, as are the factors ensuring that it occurs competently. Conversely, the factors detracting from wound healing are also examined. This general section concludes with a chapter on sutures, dressings and clinical trials. The latter underlines how much empiricism there used to be in the surgeons' approach to the planning of wounds, their closure and their care, and illustrates how far the questionable practices of the past have been replaced by the guidelines resulting from controlled trials. In the following section the reviewer found much to interest him in the section on the abdominal wall, the liver, pancreas and biliary tract, though the chapters on trauma, the urinary tract, and bone and nerve repair seemed equally informative. In a final section, Tom Hunt of San Francisco, who has contributed so greatly to our knowledge of dynamic wound healing, reflects on future trends. An important one, which he considers to be within our grasp, will be the elimination of wound infection.

Diagnostic Imaging of the Lower Urinary Tract. By M. D. Rifkin. Pp. xi + 339. New York: Raven Press. 1985. Price $58.50.

Congratulations must go to Dr Rifkin for his timely production of a new text specifically devoted to imaging of the lower genitourinary tract (for obvious reasons he excludes the female reproductive system). Against the background of the proven efficacy of ultrasound the newer technologies of CT and MRI (magnetic resonance imaging) have been introduced into the armamentarium of those interested in the lower genitourinary tract and it is about the current scope, the merits and demerits of the several modalities that this book has been written.

To remind us of basics, there is a useful introductory section on the embryology and anatomy of the male genitourinary tract. Special emphasis is placed on a cross-sectional approach which is essential to the understanding of ultrasound, CT and MRI images. There follows a long chapter on the urinary bladder. The relative roles of the different techniques are discussed and much emphasis is placed on the staging of bladder tumours. As yet, there is no really reliable technique available. Unfortunately the situation is little better in the prostate, where modern technology has failed to come up with a consistently reliable imaging method for distinguishing between benign and malignant disease. Accurate staging of carcinoma is improving, however, and radioisotope bone scanning provides an excellent method of monitoring the progress and response to therapy of skeletal metastases. The chapter dealing with the urethra and penis introduces some fascinating sagittal linear transrectal ultrasound images of the bladder neck and posterior urethra. These structures may be viewed in "real time" during micturition and this technique will obviously be of future interest to those involved in urodynamics.

The final section includes the scrotum and it is here that ultrasound, together with radioisotope scanning, appears to be a diagnostically effective combination.

The text is liberally illustrated with line drawings and a variety of generally well produced images. Reading between the lines, one has the impression that high technology is still not answering a lot of the questions posed by the urologist and Dr Rifkin does not always perhaps put enough emphasis on what cannot be done. Nevertheless, this will prove a transiently useful book and one message that does come over is that if you have to compromise and settle for one modality only in this field, ultrasound at present will give more answers to more questions than any other single technology.

Urologic Endoscopy. A Manual and Atlas. By D. H. Bagley, J. L. Huffman and E. S. Lyon. Pp. ix + 291. Boston/Toronto: Little, Brown & Co. 1985. Price US $95.00.

The authors rightly justify their book because of the "explosion in urologic endoscopy" due to the use of endoscopic techniques throughout the urinary tract. The contents are comprehensive and topical, ranging from routine cystourethroscopy, resections and endoscopic removal of bladder stones to the more recent ureteropyeloscopy and percutaneous techniques. There are useful chapters on chromocystoscopy, brush biopsy of the upper tract and photography as well as basic procedures on irrigation and the care of instruments. It is a well prepared and well illustrated book that can be highly recommended for libraries and urological departments.

Urologic Injuries. By W. G. Guerriero and C. J. Devine, Jr. Pp. vii + 197. Hemel Hempstead: Prentice/Hall International. 1984. Price £36.05.

This is a practical account of injuries of the kidney, ureter, bladder, urethra and male genitalia and includes brief chapters on acute renal failure and on the management of patients with multiple injuries. It is written for residents in training, urologists and for non-urologists who must treat abdominal or pelvic trauma and who may be confronted by urological injury when a trained urologist is unavailable. This book can be recommended as a concise, thorough, practical and well illustrated account of the subject.

Percutaneous Surgery of Kidney Stones. Techniques and Tactics. By K. Korth. Pp. x + 96. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1984. Price DM88,-; approx. US $32.10.

This short, profusely illustrated book provides a basis of percutaneous surgery for renal stones. In the chapter entitled "Puncture of the Kidney" the author states that "the art of laying a good percutaneous track is probably the most important prerequisite for the success of a percutaneous kidney stone operation." It is very difficult to teach this art from a textbook, however clearly the technique is illustrated. The book is recommended to those who do not possess a textbook on percutaneous surgical techniques; for those who already have such a book it is doubtful whether this publication contains sufficient new information to justify purchase.

Composición y Estructura de los Cálculos Renales. By L. Cifuentes Delatte. Pp. xii + 226. Barcelona: Salvat Editories. 1984.

This book must be the definitive work on the composition and structure of renal calculi in the Spanish language. It is most beautifully illustrated with magnificent photographs in colour as well as black and white which demonstrate with astonishing clarity (electron microscopic photos are one of the magnifying techniques used) the shape and size of the crystals of every imaginable variety of human urinary calculi.

In particular, the demonstration of the change in the form of the crystals of the dihydrate to the monohydrate of calcium oxalate, which comes about as a result of spontaneous fragmentation, is most instructive. There is an exceptionally full bibliography, a considerable proportion of which is from English language publications. For those interested in the subject of calculus disease, this book will be a happy companion on their library shelf.

Manual of Vascular Access, Organ Donation, and Transplantation. (Comprehensive Manuals of Surgical Specialities). Edited by R. L. Simmons, M. E. Finch, N. L. Ascher and J. S. Najarian. Pp. xvii + 340. New York, Berlin, Heidelberg, Tokyo: Springer-Verlag. 1984. Price DM 580,-; approx. US $211.20.

This book is especially remarkable for the excellent illustrations—all by the same artist. As the title indicates, it is a manual of vascular access, multi-organ donation and multi-organ transplantation. The contents are therefore comprehensive, with detailed descriptions and drawings for all transplant procedures. This then is a volume for a wide audience and of relatively less value for anyone seeking details of only kidney transplantation. Although it is very expensive it is a book of high quality and interest. It is strongly recommended for major medical libraries.

Proceedings of the European Dialysis and Transplant Association—European Renal Association. Volume 21. Edited by A. M. Davison and P. J. Guillou. Pp. xxvi + 1080. London: Pitman. 1985. Price £45.00.

This Proceedings is more nephrological and less transplant-orientated than previous volumes and reflects the emphasis of this Association. It is, however, still the reference source for the "Combined report on regular dialysis and transplantation in Europe" and also the "Combined report on regular dialysis and transplantation of children in Europe". These reports are full of interest and information and give a good idea of trends and management as well as transplant survival rates.

Progress in Reproductive Biology and Medicine, Volume 10. Maldescensus Testis: Operative Andrology 2. Edited by A. Kelami and J. P. Pryor. Pp. viii + 174. Basel: Karger. 1984. Price SFr. 166.-; DM 199.-; US $99.50.

This is an interesting book with a wealth of retrospective statistical information. It will be of great interest to those specialists who are making a study of testis maldescent. Many of the fundamental questions, however, remain to be answered. What protection against subsequent malignancy may we hope to gain following orchiopexy before the age of 6 years? What is the degree of risk for subsequent malignancy for the opposite testis in the unilateral case? What is the role of testis biopsy to screen such cases for carcinoma *in situ*? What is the true effect of testis maldescent on subsequent fertility? Many of the articles address these questions but since most of the information is retrospective the answers are still vague. The sentence in the chapter by Westenfelder on the risk of malignant change perhaps summarises the dilemma: "On the whole we are left with very little help from statistical calculations in our decision to treat patients with undescended testes". Long-term prospective studies are needed: no doubt the advent of computerised linked record systems will enable this objective to be achieved in the future. There is a welcome short chapter on the use of the laparoscope to assess the intra-abdominal testis; this is almost certainly a technique worthy of wider use. On the whole this is a book for the superspecialist.

Benign Prostatic Hypertrophy. Edited by F. Hinman, Jr. Pp. xxviii + 1097. Berlin, Heidelberg, New York: Springer-Verlag. 1983. Price DM 260,--; approx. US $107.40.

Benign prostatic hypertrophy is the urologist's life blood, dominating urological training and practice. Those surgeons who adopt a mainly pragmatic approach to the management of this condition may choose to ignore this book in the belief that their knowledge is already sufficient to cope with its treatment. They would be wrong to do so, for it contains a wealth of information on every aspect of BPH.

The editor has produced, with the aid of nine section editors of international standing, a superb book which deserves to become the definitive work on this subject. All conceivable topics are covered, from Historical Aspects to the Future of Surgery and embracing chapters on endocrine control and more practical areas such as antibiotic usage. There are some areas which will be new to the British urologist—many of them curiosities such as Prostatic Obstruction in Chinese and a Method for Establishing Fees—but throughout this book there is much to stimulate and enjoy.

The layout is excellent and the clarity of typeface and diagrams combine with good editorial control to make this an easy book to read. There appear to be few errors in the text but the style of citing references is inconsistent and there are a couple of obvious errors.

Every urological department should own a copy of this book, which should be essential reading for trainees for whom the separate section of annotated bibliography will provide ready access to the key papers on every aspect of the subject.

The book is dedicated "To my father—I think he would have enjoyed this book". I am sure he would have done.

Transluminal Angioplasty. Edited by W. Castañeda-Zuñiga. Pp. vii + 207. Stuttgart: Georg Thieme Verlag. 1983. Price DM 148,--.

This book provides an excellent and authoritative update on this rapidly growing, inherently simple method of treating certain forms of occlusive vascular disease. The contributors have been carefully chosen and are mostly well known experts in this field. Almost all areas in which percutaneous angioplasty is used (including some of its most recent applications) are considered. Of particular interest to the urologist is a comprehensive and detailed section on angioplasty in the management of renovascular hypertension (including transplant renal artery stenosis). There is also a short chapter outlining early experience of transluminal angioplasty in the management of vasculogenic erectile impotence. The text is generally concise and easy to read. The book is well illustrated throughout and is a useful source of references on this rapidly developing subject.

Physicians, surgeons and radiologists concerned with occlusive vascular disease and its management will find this an interesting and informative little book.

Post-operative Thrombo-embolism. Frequency, Etiology, Prophylaxis. By D. Bergqvist. Pp. x + 230. Berlin, Heidelberg, New York: Springer-Verlag. 1983. Price DM98,--: approx. US $42.30.

The last 15 years have seen a tremendous growth in knowledge of the natural history of post-operative deep vein thrombosis and how it may be prevented. So large is the literature in the field and so varied the prophylactic methods that it may be difficult for a surgeon to decide whether prophylaxis is advisable and what method might be appropriate in his practice. This is particularly likely to be true if he works in a field other than general surgery and orthopaedics, where most of the major trials have been conducted. This book can provide the answers.

It is aimed not only at those specifically interested in haemostasis but also serves as a reference text for any clinician who would like an update in the field. There are sections on the history of knowledge of thrombosis, frequency, diagnostic methods, pathogenesis and analysis of risk factors, but the greater part of the book (two-thirds in fact) deals with prophylaxis. A valuable feature is the way it is divided into specialty sections so that the urologist, for example, with the help of an excellent index can quickly sift out the information germane to his specialty. Thus evidence is provided that the risk of deep vein thrombosis is 3 times greater with transvesical prostatectomy than with transurethral resection. The incidence of radio-iodinated fibrinogen detected deep vein thrombosis in mixed urological populations ranges from 25 to 59%. It was interesting to learn that it has been shown that plasminogen activator production decreases after transvesical prostatectomy but not after transurethral resection. Several authors have shown pulmonary embolism to be the commonest cause of death after prostatectomy. The pros and cons of low dose heparin, dextran and calf muscle compression in all branches of surgery, including urology, are fully covered. A remarkable amount of information has been packed into a compact volume. The author must have an excellent bibliography retrieval system: there are approximately 1700 references. This book is warmly recommended.

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Kidney, Small Proteins and Drugs. Contributions to Nephrology, volume 42. Edited by C. Bianchi, A. Bertelli and C. G. Duarte. Pp. x + 261. Basel: Karger. 1984. Price S Fr 125.-; DM 150,-; US$75.00.

Disputed Issues in Renal Failure Therapy. Contributions to Nephrology, volume 44. Edited by M. J. Lysaght, E. Wetzels and H. J. Gurland. Pp. xi + 294. Basel: Karger. Price S Fr 98.-; DM 117,-; US$41.75.

Proceedings of the European Dialysis and Transplant Nurses Association. Volume 13. Edited by Elizabeth Stevens and Patti Monkhouse. Pp. xi + 242. London: Pitman. 1985. Price £12.50.

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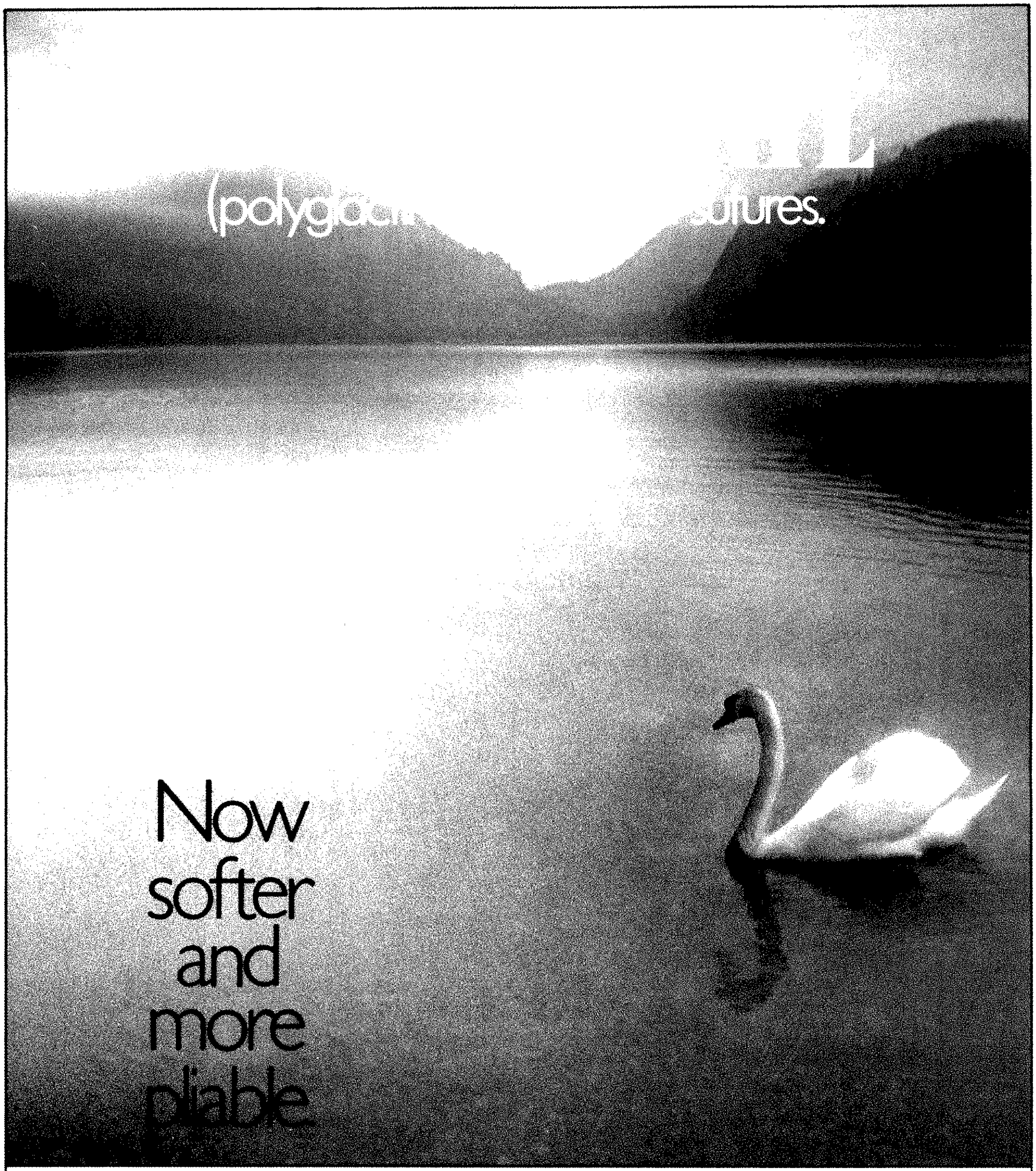

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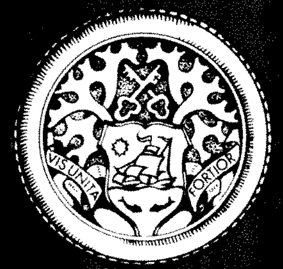

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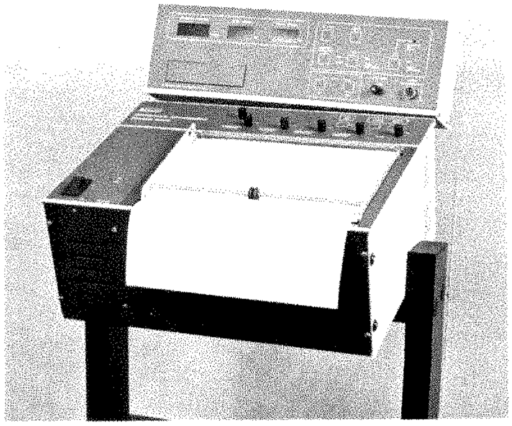

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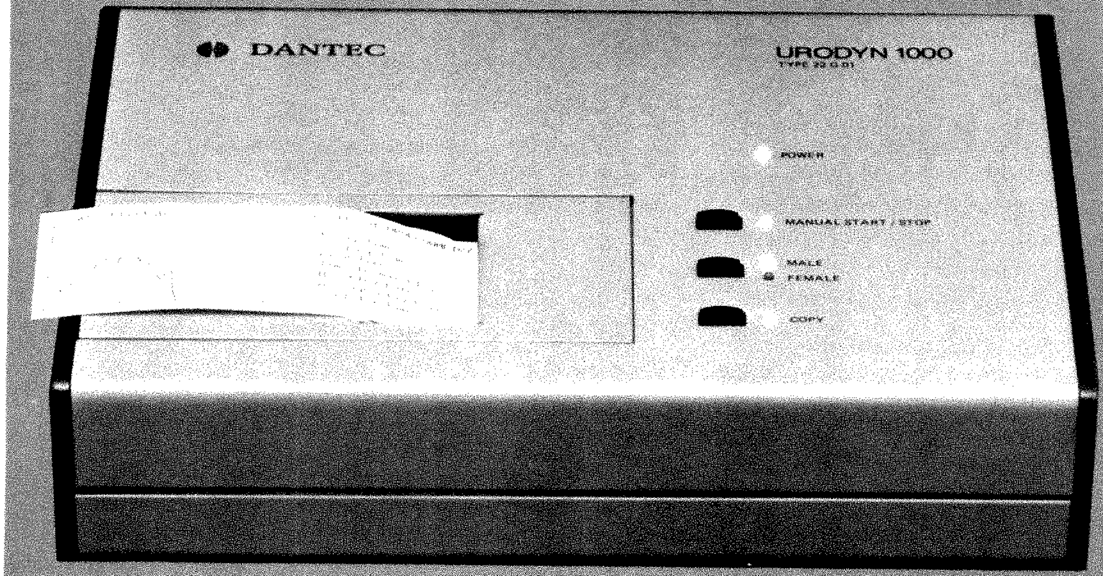

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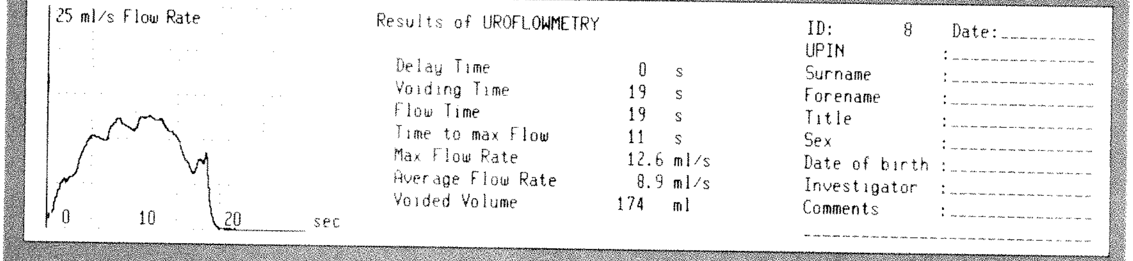
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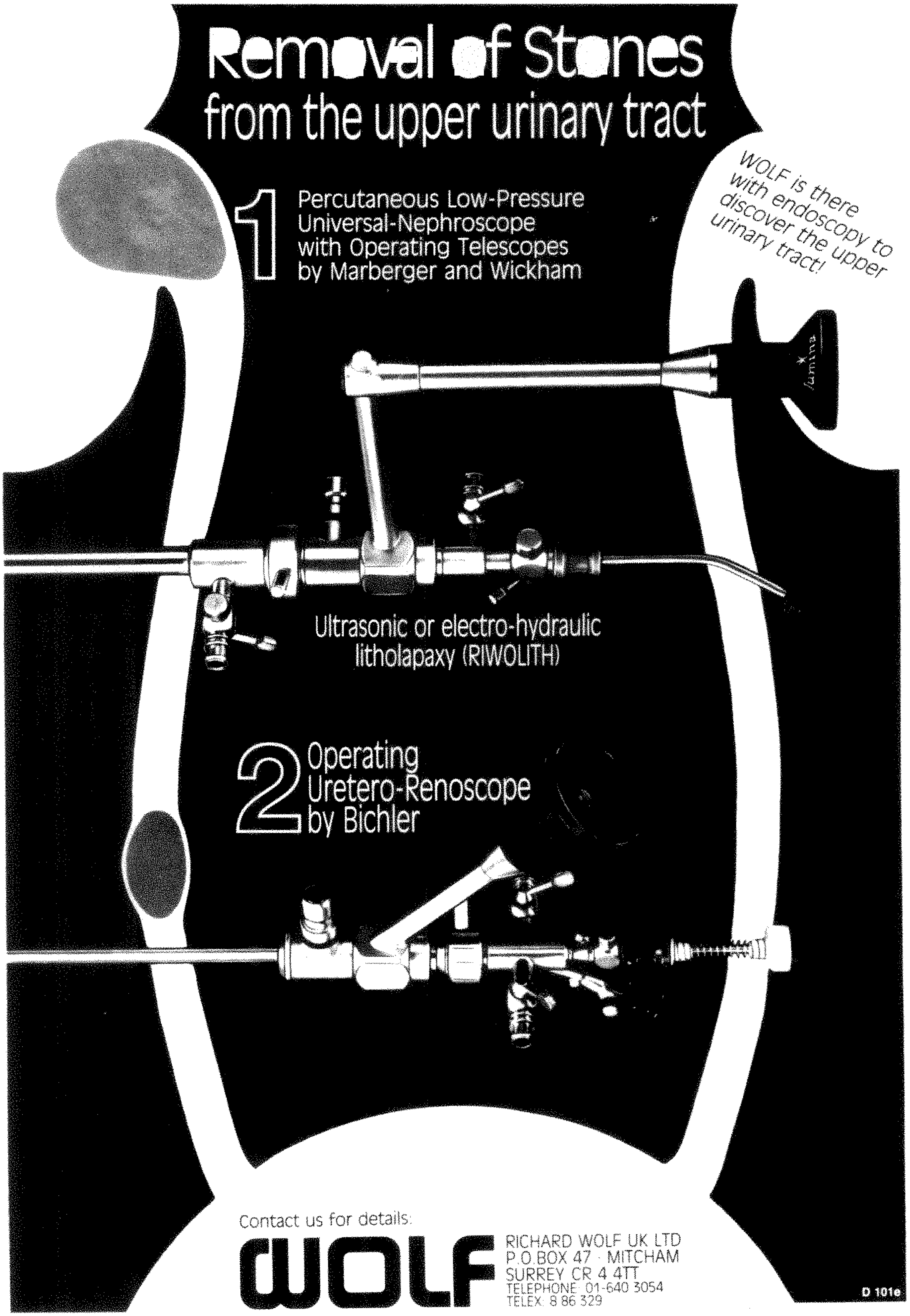

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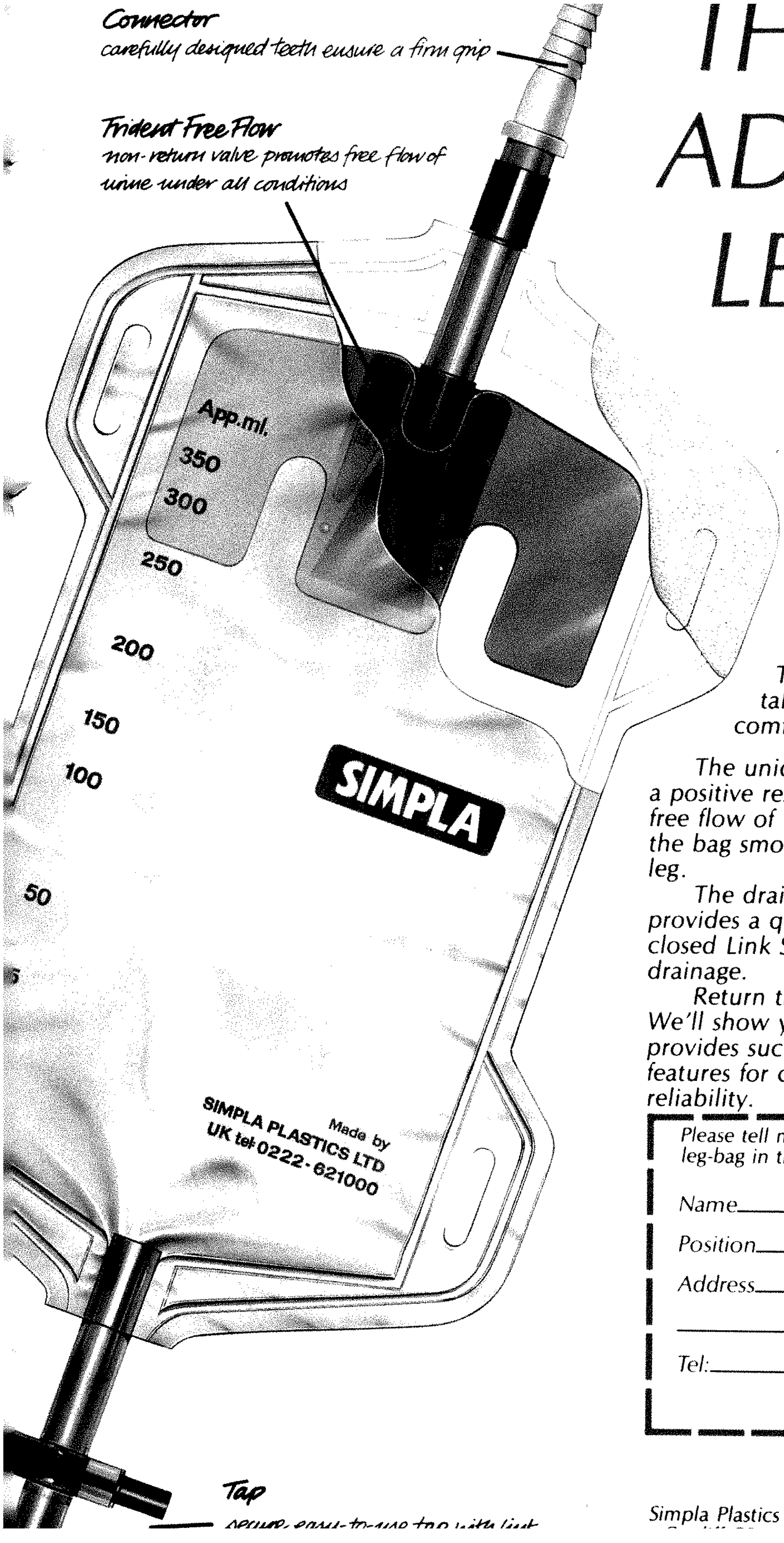
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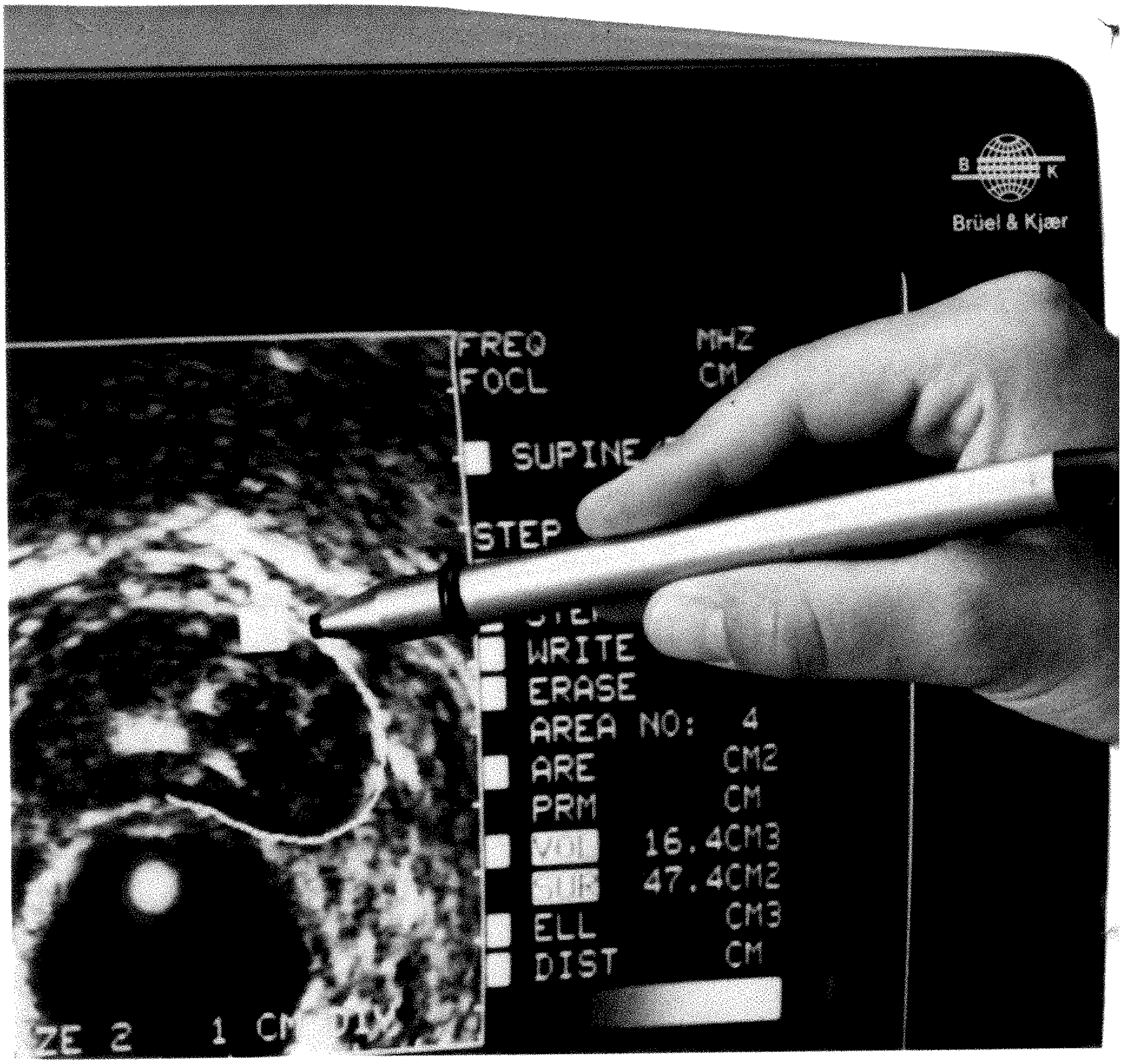
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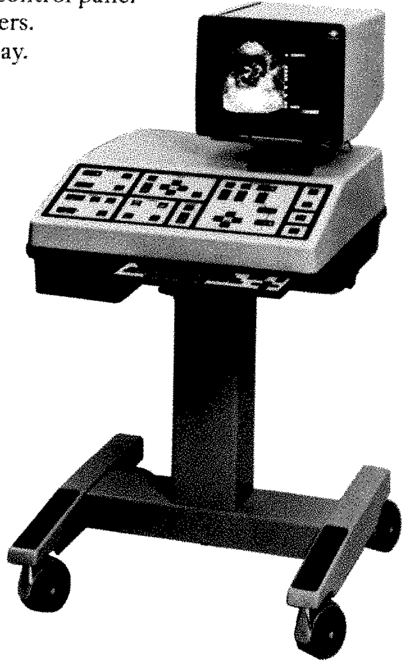

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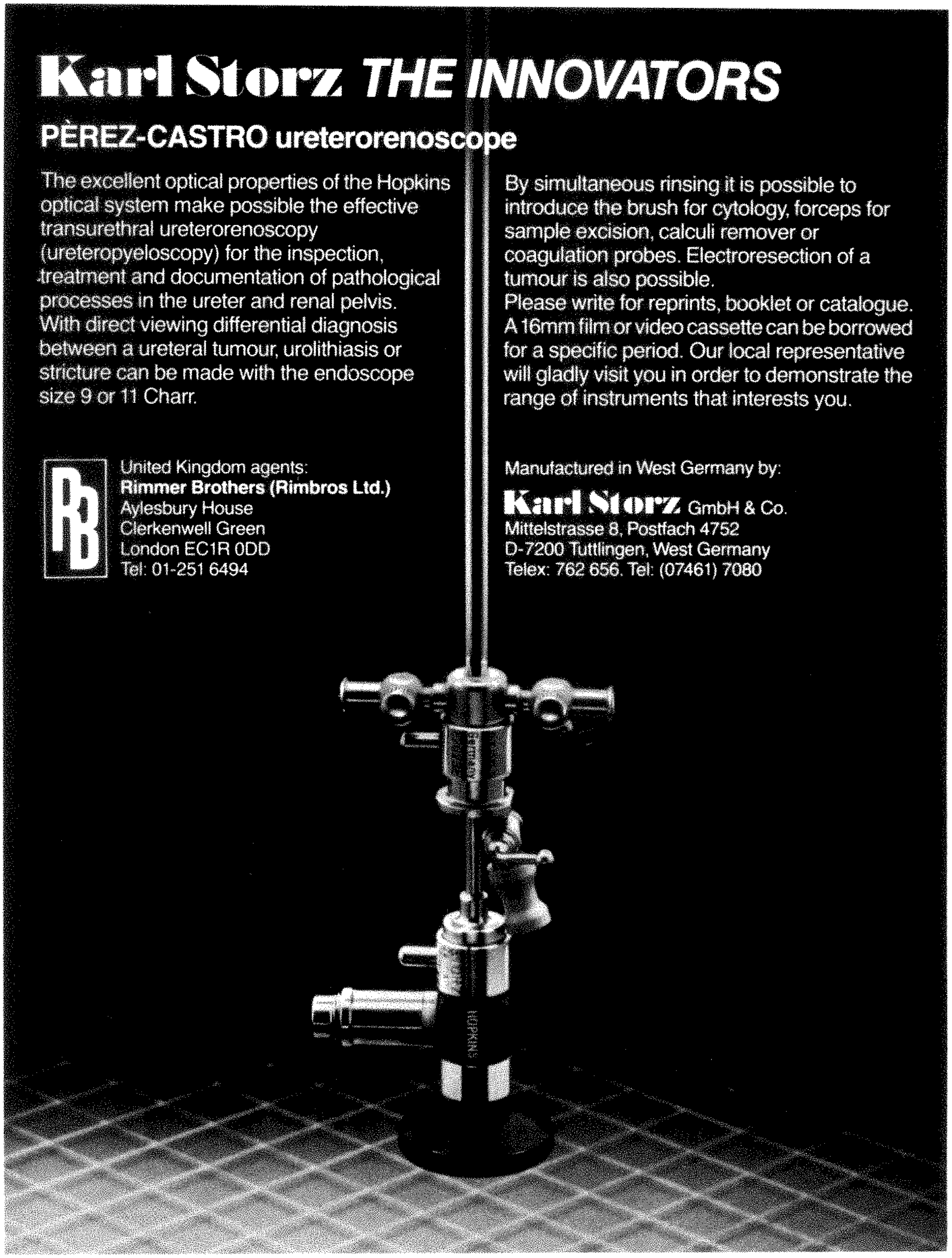

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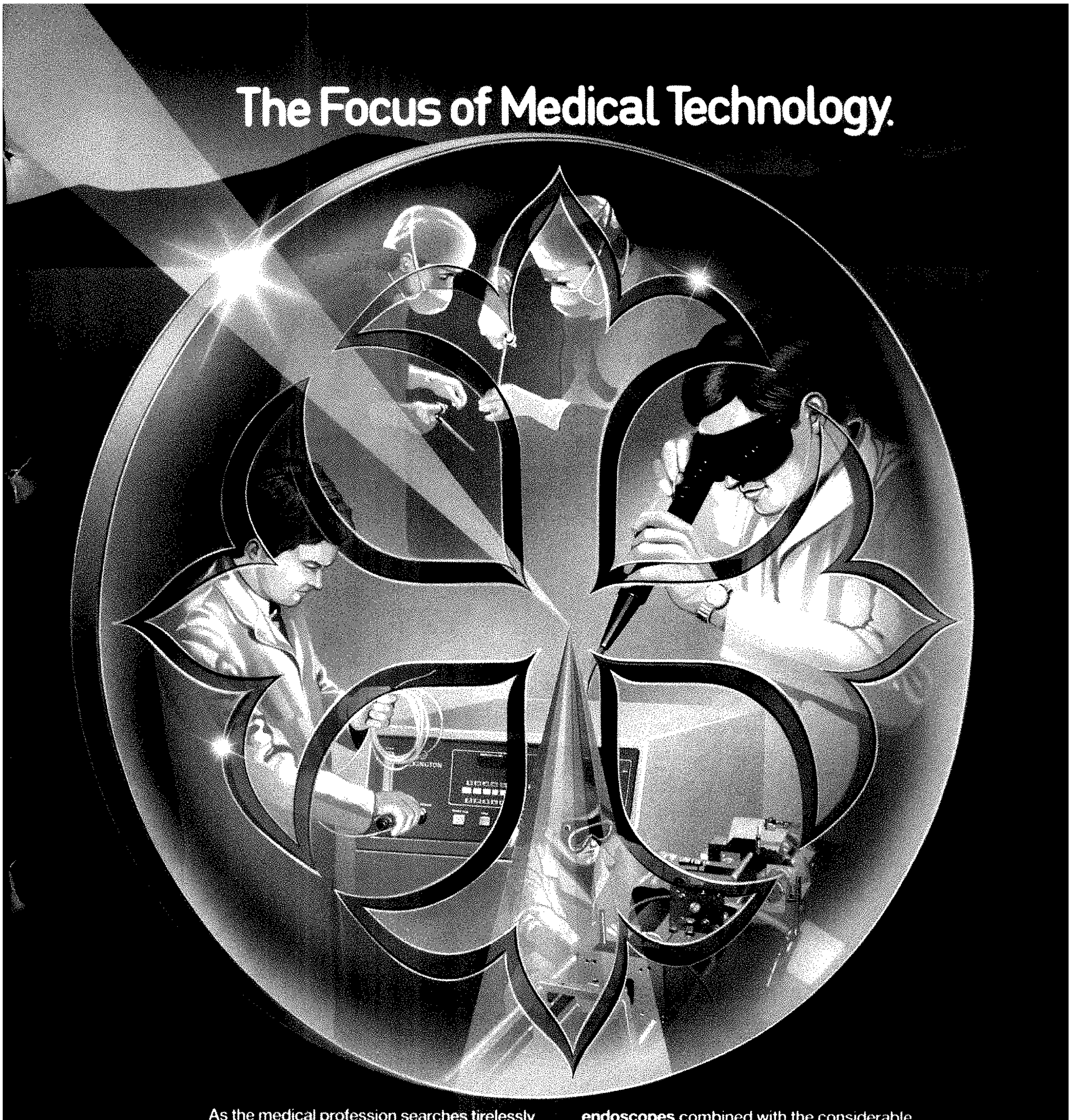

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British Journal of Urology (1985), **57**, 603-604

Percutaneous Nephrolithotomy

A Report of 150 Cases

H. N. WHITFIELD and V. A. MILLS

Department of Urology, St Bartholomew's Hospital, London

Summary—One hundred and fifty patients with renal stones have been treated by percutaneous nephrolithotomy. Complete stone clearance was achieved in 130 cases (87%). The management of patients in whom stone removal was not achieved percutaneously and the complications of the procedure are discussed. Guidelines are set out for successful percutaneous nephrolithotomy.

During the past 3 years the superiority of percutaneous nephrolithotomy (PCNL) over conventional open surgery for renal stones in terms of morbidity, length of hospital stay, convalescence and cost effectiveness has been established (Wickham and Kellett, 1981; Whitfield, 1983 a and b; Brannen *et al.*, 1985). Radiological techniques have been developed, so that an accurately placed transparenchymal nephrostomy track can be established reliably, rapidly and safely. The purpose-built instruments which have been manufactured for stone destruction and removal have increased the success rate of the procedure, so that 90% of all renal stones can now be removed percutaneously.

In this study the results of the first 150 cases of percutaneous nephrolithotomy are reported and, on the basis of the experience gained, guidelines are suggested which will accelerate the learning curve for those who are embarking on the technique.

Patients and Methods

The ages of the 150 patients (109 male, 41 female) ranged between 18 and 77 years. One hundred and five stones were in the renal pelvis, 38 were caliceal and 7 were in the ureter. Ninety-nine cases were two-stage and 51 were one-stage procedures.

Puncture of the pelvicaliceal system was made with a Longdwell needle, using local anaesthesia and sedation in all of the two-stage procedures and general anaesthesia in all but one of the one-stage procedures, in which an epidural anaesthetic was given.

The collecting system was outlined after intravenous contrast (89 cases), after retrograde ureterography (53), following antegrade pyelography (7), or using uretero-ileal reflux (1). After initial unsatisfactory results using telescopic metal bougies and balloon catheters over floppy guide-wires, most tracks were established by using graded teflon dilators over a stiff guidewire with a 5 to 10 cm flexible tip. The tracks were dilated to 26 to 30 F and the average interval between the first and second stages in patients undergoing a two-stage procedure was 72 h. Track patency was secured by a 26 F Porges nephrostomy tube anchored by an inner co-axial 10 F pigtail catheter.

A variety of instruments was used for stone extraction, but with the introduction of purpose-built nephroscopes the preferred methd was to use the working element of a nephroscope and a straight alligator or triradiate grasping forceps through an Amplatz sheath. Stones too large to be extracted intact were disintegrated ultrasonically

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Presented at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

(35 cases) or electrohydraulically (7 cases). PCNL was combined with extracorporeal shockwave lithotripsy (ESWL) in four patients. A 26 F nephrostomy tube was left *in situ* post-operatively overnight, or longer if haematuria had not settled. Prophylactic antibiotics were administered to all patients.

Results

Ninety-eight of the 105 pelvic stones (93%), 27 of the 38 caliceal stones (71%) and five of the seven ureteric stones (71%) were removed completely, an overall success rate of 130 of 150 cases (87%). Residual caliceal fragments remained in three patients with pelvic stones and in one patient with a large caliceal stone, all of which had required disintegration. Three patients with residual caliceal fragments have remained asymptomatic and no further treatment has been undertaken, but in the fourth patient the residual stone enlarged rapidly and was removed percutaneously. Fragments from the disintegration of a pelvic stone blocked the ureter of one patient and had to be removed at open surgery. The mortality in this series was nil. No patient required nephrectomy or open surgery for any complication of the procedure, but 12 patients underwent open surgery for stone removal when PCNL was unsuccessful (4 pelvic, 6 caliceal and 2 upper ureteric stones). There were four patients with caliceal stones which were not removed by PCNL who elected not to undergo open surgery.

Three patients whose stones were infective in origin developed septicaemia which responded well to parenteral antibiotics. Three patients required blood transfusion, one for bleeding at the time of track dilatation, one for bleeding following stone removal and one patient returned to hospital on the tenth post-operative day with a secondary haemorrhage.

A "TUR" type reaction occurred in two patients at a time when glycine was being used as the irrigating fluid and before the introduction of the Amplatz sheath. In one of these patients the amount of extravasated fluid was sufficient to cause respiratory distress and mechanical ventilation was required for 24 h post-operatively.

Discussion

The percentage success rate has increased from 70 to approximately 90% as experience has been gained in both the urological and radiological stages of the procedure. Better instrumentation and improved case selection have also contributed to the improved success rate. Staghorn calculi, upper pole caliceal stones, high kidneys, duplex collecting systems and multiple stones all remain relative but not absolute contra-indications to the procedure.

Although ESWL can resolve some of these difficulties, the technique itself creates problems of its own. Experience from stone centres in this country and elsewhere has served to emphasise that PCNL and ESWL are mutually dependent (Wickham *et al.*, 1985). It is likely that the availability of ESWL in the United Kingdom will remain restricted for some time to come; in the meanwhile, since 90% of all patients with stones can be treated by PCNL, it can only be to the advantage of patients with renal stones for the technique to be adopted by all departments of urology.

It is recommended that, until experience is gained, the procedure shoud be performed in two stages, separated by an interval of 72 h. Initially, only pelvic stones not requiring disintegration and which are situated within a moderately dilated pelvicaliceal system should be attempted. Track dilatation is easiest using graded teflon dilators over a stiff guidewire. The stone should be removed using rigid forceps and a purpose-built nephroscope rather than a wire basket introduced via a cystoscope. Caliceal stones are usually best removed as a one-stage procedure.

The low morbidity now associated with PCNL makes it hard to justify conventional open surgery for anything other than complex stones.

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The Authors

H. N. Whitfield, FRCS, Consultant Urologist.

V. A. Mills, formerly Senior Radiographer. Now Superintendent Radiographer, Royal United Hospital, Bath.

Requests for reprints to: H. N. Whitfield, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Percutaneous Coagulum Nephrolithotripsy: a New Approach

R. HASUN, P. C. RYAN, A. B. WEST, J. M. FITZPATRICK and M. MARBERGER

Departments of Urology, Rudolfstiftung, Vienna, Austria, and Meath Hospital, Dublin, Ireland

Summary—Intrarenal scatter of stone fragments during percutaneous nephrolithotripsy is a complication which may predispose to post-operative pain and further stone formation. The use of a coagulum to prevent such a complication has proved difficult when introduced percutaneously. This experimental study describes a new gelatine (Lithogel®) which is introduced through the nephroscope to coat the renal calculus; it allows easy disintegration of the calculus within the gel, is safe to use and effectively prevents the scatter of fragments into inaccessible calices.

With a success rate of 92%, percutaneous lithotripsy of renal calculi has proved to be a highly effective and safe form of treatment with minimal morbidity (Marberger *et al.*, 1985). Residual stone fragments have been a problem and this occurs most often with larger stones requiring intrarenal disintegration. A coagulum formed around the stone would theoretically prevent dispersal and scattering of the fragments and facilitate complete removal (Watson *et al.*, 1983). Clots formed of blood derivates carry a risk of pulmonary embolism (Pence *et al.*, 1982), clotting disorders (Watson *et al.*, 1983), obstruction from residual clots (Klosterhalfen *et al.*, 1969) and viral contamination (Rathore and Harrison, 1976), which renders their use in percutaneous surgery hazardous. The present study was made to develop and test a material designed to avoid these problems.

Materials and Methods

After *in vitro* testing of various gelatine agents, a partially hydrolysed collagen formed of chemically identical protein chains with molecular weights of 25,000 to 300,000 (Lithogel®, Farco Pharma, FRG) was chosen. It liquefies to the properties of plasma at 37°C but turns to a clear gel of high tensile strength at lower temperatures (Fig. 1). Produced from porcine protein, it is non-toxic, chemically stable, easy to sterilise and reasonably priced. Similar gelatines are used for alimentary purposes, as plasma expanders, for haemostatic sponges, and for medical lubrication purposes (Wade, 1980). An *in vivo* intravenous toxicity test of the agent in rats revealed no evidence of significant acute toxicity (Hübscher, 1984). At i.v. injection the minimal toxic dose was 26.1 ml/kg body weight, the lowest lethal doses 38.3 ml/kgBW and the LD50 42.8 ml/kgBW. The LD100 could only be hypothesised by extrapolation of the other results, since it proved technically impossible to inject such a large i.v. dose in rats. The rats succumbing to overdoses died within 5 min of injection, obviously from volume overload. If they survived the first 5 min, they recovered completely within the next 60 min. The agent was packed in 10 ml syringes, sterilised by gamma irradiation and warmed to 37°C prior to the experiment.

Using the model described by Webb and Fitzpatrick (1985), 20 adult mongrel male dogs weighing 20 to 25 kg were anaesthetised with pentobarbital (30 mg/kgBW i.v.), intubated and well hydrated with i.v. saline. The left kidney was exposed via a flank incision. Supporting the kidney manually, a nephrostomy track was then established from the lateral convexity of the kidney, using a fine needle technique. The track was dilated

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

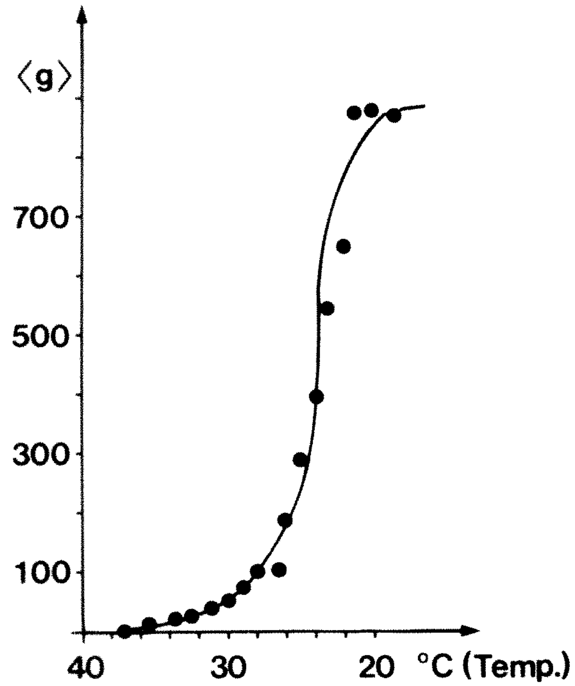

Fig. 1 Bloom strength (weight applied to a plunger 12.7 mm in diameter to produce a depression in gel 4 mm deep) as an index of clot solidity in relation to temperature.

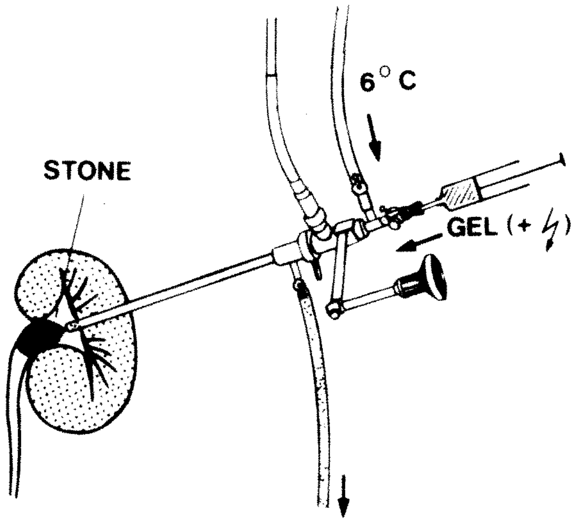

Fig. 2 Method of insertion of gel into the dog kidney and coating of the calculus; a cold perfusion of 6°C solidified the gel once it surrounded the calculus.

with metal telescope dilators and the 24F Wolf nephroscope introduced. A human calcium oxalate stone about 8 mm in diameter was introduced into the pelvis and, depending on the size of the collecting system, 1 to 5 ml gel were injected into the system around the stone (Fig. 2). By irrigating the system with saline cooled to 6°C at a flow rate of 15 ml/min a solid clot encasing the stone formed within 1 to 2 min. Advancing a 9F electrode through the gel, the stone was then disintegrated with the Wolf electrohydraulic lithotrite as described by Webb and Fitzpatrick (1985). All clots and retained fragments were removed with forceps.

Arterial blood pressure, pulse rate, rectal temperature and urine output were monitored continuously during the operation. Blood specimens were withdrawn for gas analysis, clotting screens, blood count and biochemistry every 15 min.

Seven dogs were sacrificed after 3 h, three after 3 days, four after 7 days and six after 28 days. In the acute group, lung and heart were removed *en bloc* and an *ex vivo* pulmonary angiogram was obtained: one dog also underwent *ante mortem* digital subtraction angiography of the lungs and another a pulmonary and renal DMSA scan. All dogs in the chronic group had an *ante mortem* split creatinine clearance and intravenous urogram; three dogs had a *post mortem* Micropaque angiogram of both kidneys and the kidneys of nine dogs were studied with Microfil or Methacrylate corrosion casts. A *post mortem* contact radiograph was obtained from all kidneys and a precise autopsy with histology of lungs and macroscopic and microscopic autopsy was performed on all dogs.

Results

One dog died in the post-operative recovery period; this animal had required almost twice the usual pentobarbital dosage during the experiment and was acidotic, but had otherwise not shown any abnormality. As autopsy revealed no abnormal findings, in particular no evidence of pulmonary embolism, death was attributed to an overdose of pentobarbital. All other dogs showed a normal intra- and post-operative course.

Some metabolic acidosis was usually noticed at the end of the operation, but otherwise all physical and laboratory indices stayed within the normal range. There was no evidence of adverse effects on circulatory, pulmonary or renal function, on electrolyte metabolism or the clotting system (Fig. 3). Rectal temperatures dropped slightly to an average minimum of 36.2°C at the end of anaesthesia.

The pulmonary angiogram of one of seven dogs showed incomplete filling of peripheral vessels; precise autopsy with opening of all vessels under optical magnification revealed no emboli, so that the

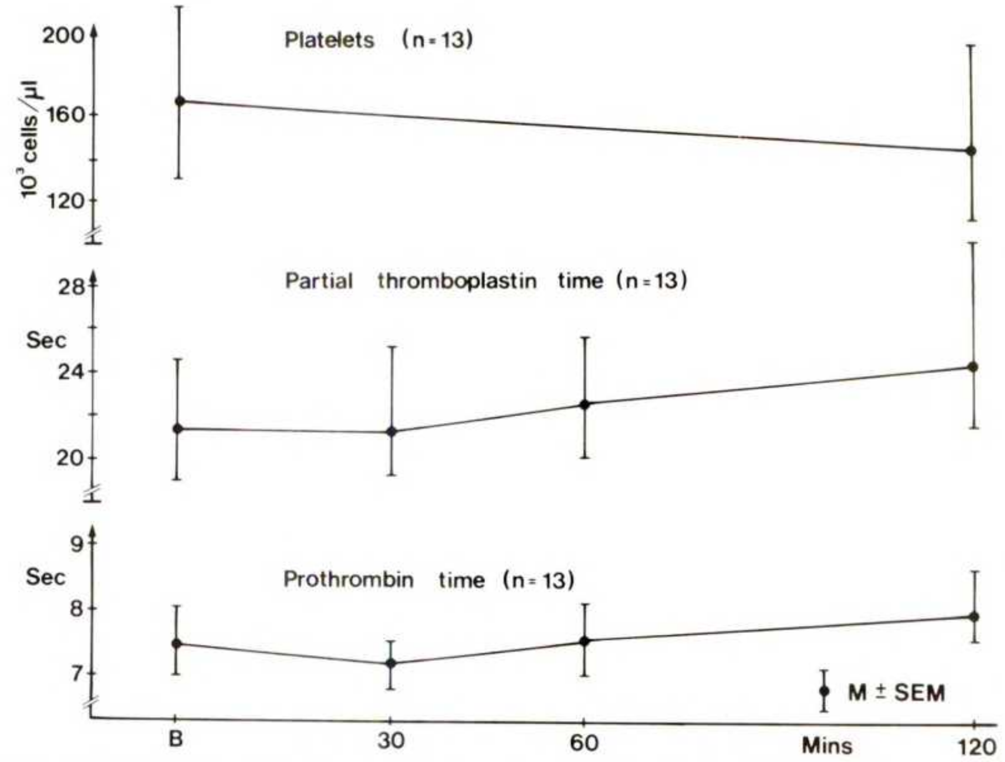

Fig. 3 Measurement of platelets, partial thromboplastin time and prothrombin time. The levels were unaffected by the lithotripsy inside the gel.

focal malperfusion obviously resulted from incomplete dye filling. All other *post mortem* pulmonary angiograms (Fig. 4), the *in vivo* digital subtraction angiography and the pulmonary DMSA scan demonstrated normal lung perfusion.

All intravenous urograms showed normal renal morphology without residual calculi, obstruction or dye extravasation (Fig. 5). Renal function as evaluated by creatinine clearance was always normal. No residual calculi were visible on the *post mortem* contact films of the kidneys, in contrast to electrohydraulic lithotripsy in the same model

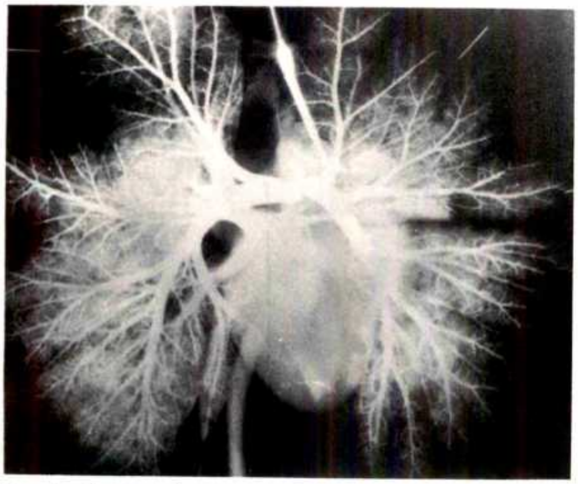

Fig. 4 *Ex situ* pulmonary angiogram following gel insertion and nephrolithotripsy; no evidence of any perfusion defect.

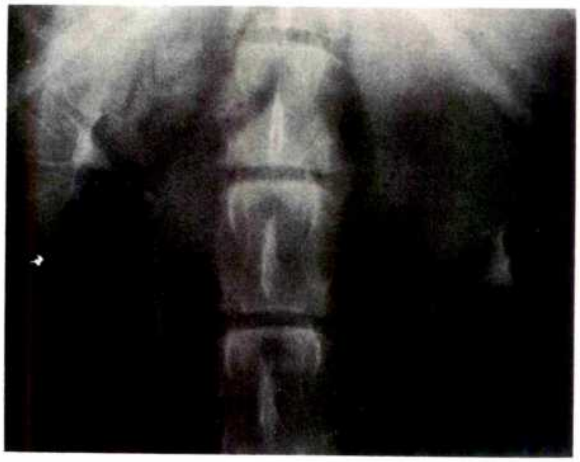

Fig. 5 Intravenous urogram following nephrolithotripsy: normal anatomy.

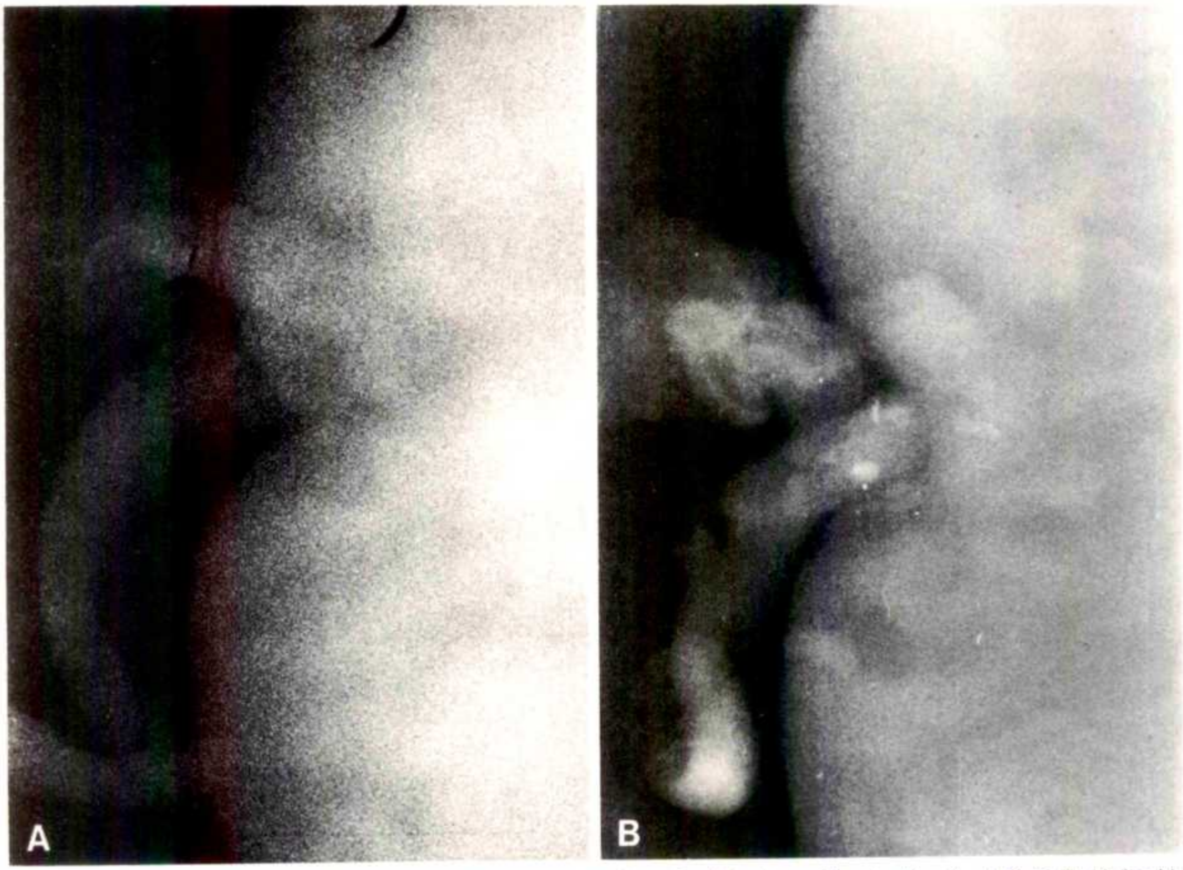

Fig. 6 (A) Intrarenal scatter of stone fragments after electrohydraulic nephrolithotripsy without gel (we thank D. R. Webb for this photograph). (B) Absence of scatter and residual fragments after electrohydraulic nephrolithotripsy using the gel.

without gel (Fig. 6) (Webb and Fitzpatrick, 1985). The completeness of stone removal was confirmed at autopsy. In addition, soft tissue damage seemed to be considerably less than after this procedure without gel protection (Webb and Fitzpatrick, 1985); no complete perforations were noted. The kidney corrosion studies and the histology of kidneys and lungs showed no abnormal findings.

Discussion

At 30°C the agent used in this study forms a solid clot that permits rapid and complete stone extraction after electrohydraulic stone disintegration. The reduction of intrarenal temperature was rapidly achieved in this *in vivo* model without a significant effect on total body temperature. At a lower temperature the tensile strength of the clot would have been even better, but attempts at this with higher flow rates rapidly resulted in clogging of the nephroscope and impaired vision. The idea of obtaining a complete cast of the collecting system with the clot, which is then extracted *in toto* with the stone fragments, as in coagulum pyelolithotomy, was therefore abandoned. By simply coating the calculus with a layer of gel all fragments were reliably retained, yet neither vision nor irrigation was impaired. Repeated electrohydraulic discharges generate heat that rapidly dissolves the gel around the probe. By continuous cold irrigation at a low flow rate this was limited to an area in the immediate vicinity of the probe, so that optical control and stone contact were facilitated, but the clot was still effective in retaining the fragments. The attenuation effect of the clot on the shock wave reduced the adverse effects of the shock wave on the surrounding soft tissue, perhaps also by smothering the blast effect of the disintegrating stone on the mucosa. When the system was irrigated with saline at room temperature the clots dissolved again within seconds. No cardiorespiratory, pulmonary or renal side effects were noted.

Because of a lower risk of damage to surrounding structures the authors routinely use ultrasonic lithotripsy for intrarenal stone disintegration and restrict electrohydraulic lithotripsy to very hard or very large calculi. Preliminary experience with the clot in the former method exposed problems with a loss of efficiency of the sonotrode because of attenuation from the clot. Ultrasonic lithotripsy also relies heavily on aspiration through the probe for cooling and removal of stone debris, and the gel tends to clog the aspiration lumen.

Acknowledgements

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The Authors

R. Hasun, MD, Resident in Urology, Rudolfstiftung, Vienna.
P. C. Ryan, FRCSI, Research Fellow, Department of Urology, Meath Hospital, Dublin.
A. B. West, MB, BCh, BAO, Registrar in Pathology, Federated Dublin Voluntary Hospitals, Dublin.
J. M. Fitzpatrick, MCh, FRCSI, Consultant Urologist, Meath Hospital, Dublin.
M. Marberger, MD, Professor of Urology and Chief, Department of Urology, Rudolfstiftung, Vienna.

Requests for reprints to: M. Marberger, Department of Urology, Rudolfstiftung, Juchgasse 25, A-1030 Vienna, Austria.

British Journal of Urology (1985), **57**, 610-612

A Strategy for Management of Upper Tract Calculus Disease

S. R. PAYNE, D. R. WEBB and J. E. A. WICKHAM

Institute of Urology and the Devonshire Hospital Lithotripter Centre, London

Summary—Extracorporeal shockwave lithotripsy, percutaneous nephrolithotomy and ureterorenoscopy now mean that approximately 98% of all renal and 85% of all ureteric calculi can be treated effectively, without recourse to open operative intervention, in centres possessing the necessary equipment and expertise. Experience with these techniques allows us to propose a strategy for the surgical treatment of upper tract stone disease.

The recent introduction of endourological techniques for stone manipulation (Wickham and Kellett, 1981; Perez-Castro and Martinez-Pinero, 1982) has revolutionised the therapeutic capabilities of the practising urologist and offered the patient methods of calculus extraction with minimal morbidity. Most recently, the advent of extracorporeal shockwave lithotripsy has been shown to be a safe and effective technique for disintegrating renal calculi *in situ* (Fuchs *et al.*, 1984). The initial price and recurring costs of the equipment do, however, dictate that only a limited number of lithotripters will be required to service a country the size of Britain; this will inevitably lead to the evolution of specialised "Stone Centres" for the management of complex upper tract calculus problems. Our experience with over 500 percutaneous nephrolithotomies, 100 transurethral ureteroscopies and 300 extracorporeal lithotripsies has led to the development of a strategy for the management of upper tract calculi in such a centre. This report describes, with use of algorithms, the management of uncomplicated renal and ureteric calculi together with those stones causing obstructive or infective complications. The methods employed for percutaneous nephrolithotomy (PCNL), ureterorenoscopy (URS) and extracorporeal shockwave lithotripsy (ESWL) have been described elsewhere (Payne *et al.*, 1985; Wickham *et al.*, 1985).

Renal Stones

The indications for intervention for renal calculi remain the same as when open surgery was the only available treatment. Stones which are present in an unobstructed urinary tract, which can be localised by bi-planar X-ray screening and which do not form a complete cast of the collecting system may be treated by ESWL alone (Fig. 1). The fragments produced by this treatment are less than 2 mm in diameter and are excreted via the ureter (Fig. 2). Lucent stones, if less than 5 mm in diameter, may be opacified by retrogradely introducing radio-opaque contrast into the renal pelvis and treating by ESWL. It can be difficult to monitor the progress of larger lucent stones using this technique and these calculi are best treated by PCNL, when all fragments may be removed under vision.

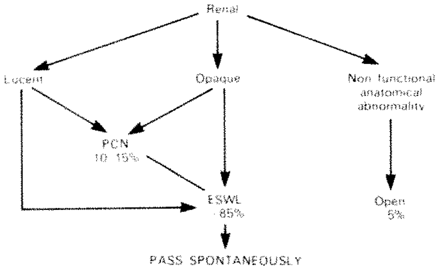

Fig. 1 An algorithm for the management of renal calculi.

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

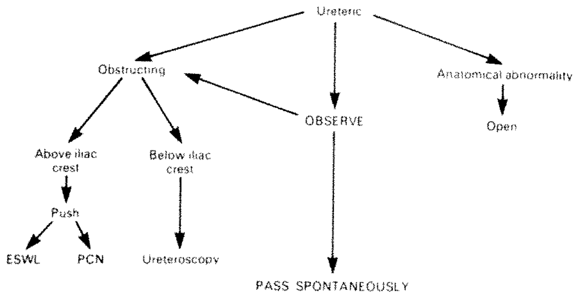

Fig. 2 An algorithm for the management of ureteric calculi.

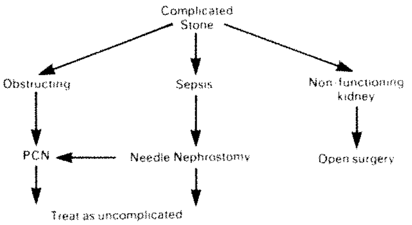

Fig. 3 An algorithm for the management of complicated upper tract stones.

Complete staghorn calculi can be fragmented by ESWL, although obstructive ureteric complications will follow treatment in almost 100% of cases. Large staghorn calculi with most of their mass in the renal pelvis should be "debulked" by percutaneous intrarenal lithotripsy to provide a space for more effective disintegration; the nephrostomy left *in situ* after PCNL decompresses the kidney, obviating infective complications and providing a conduit for the passage of stone particles. Residual stone can be treated by ESWL with the nephrostomy *in situ*.

Open surgery for renal calculi should now be reserved for staghorn calculi, where most of the stone is in narrow necked calices and when abnormalities compromising urinary outflow are present. These staghorn calculi cannot usually be debulked satisfactorily using a single percutaneous track. An extended pyelolithotomy and multiple radial nephrotomies performed as a single procedure is probably preferable.

Ureteric Stones

Small ureteric calculi should be managed conservatively unless they are complicated, long-standing or associated with a ureteric anomaly (Fig. 2). Stones larger than 5 mm in diameter which are below the pelvic rim and not causing symptoms may also be treated in this conventional way. Symptomatic calculi below the pelvic brim are dealt with ureteroscopically, the calculus being removed intact or disintegrated *in situ* with ultrasonic or contact electrohydraulic lithotripsy. Stones in the intramural part of the ureter are best removed via a meatotomy of the ureteric orifice. Calculi larger than 5 mm and above the pelvic brim are likely to become complicated and should be manipulated back into the renal pelvis with a retrograde catheter (Kellett *et al.*, 1985) and treated as renal calculi with PCNL or ESWL. This has become our standard policy for all high ureteric calculi because of our comparatively poor results with ureteroscopic manipulation (Ford *et al.*, 1984) and poor disintegration of ureteric calculi when treated *in situ* with ESWL (Chaussy *et al.*, 1980). Stones larger than a centimetre, especially if present for more than 3 months, are usually impossible to manipulate retrogradely due to mucosal embedding and may be removed percutaneously or by open surgery. Correction of anatomical abnormalities below the stone is required in the remainder of the 15% of patients who require open ureteric surgery.

Complicated Stone

Urinary calculi which are complicated by infection or obstruction are converted to a "stable state" by decompression prior to elective treatment of the underlying stone. Proper evaluation of the anatomy and function of the kidney following decompression is essential to formulate a plan of management for the calculus; the anatomy is best defined by an antegrade nephrostogram and function should be evaluated by radionuclide renography in cases where poor function remains after a period of drainage.

Needle nephrostomy has little morbidity when performed under antibiotic cover, although prolongation of antibiotic treatment may be necessary if this track is dilated to facilitate the drainage of thick pus. Once a stable state has been attained the calculus can be removed by an appropriate technique (Figs 1 and 2). If baseline renal function has, however, been shown to be less than 15%, once a stable state is reached we would consider nephrectomy as the procedure of choice.

Discussion

A combination of PCNL, URS and ESWL enables upper urinary tract calculi to be treated with minimal morbidity and tremendous cost effectiveness (Wickham *et al.*, 1983; Miller *et al.*, 1984). None of these newer modalities of treatment is, however, without complication (Payne *et al.*, 1985; Wickham *et al.*, 1985) and they should not be applied without appropriate indication. PCNL and URS are essential techniques for the less invasive treatment of calculi that may not be treated by ESWL alone or in combination and are mandatory for dealing with the obstructive complications of extracorporeal lithotripsy. By combining these skills, open operative intervention for upper tract calculi should be limited to lithotomy associated with non-functioning kidneys, structural drainage abnormalities and staghorn calculi with most of their bulk in the periphery of the kidney.

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The Authors

S. R. Payne, FRCS, Lecturer in Percutaneous Renal Surgery, Academic Unit, Institute of Urology.

D. R. Webb, FRCS, Urologist, Devonshire Hospital Lithotripter Centre.

J. E. A. Wickham, MS, FRCS, Director of Academic Unit, Institute of Urology.

Requests for reprints to: J. E. A. Wickham, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Relationship of Stone Growth and Urinary Biochemistry in Long-term Follow-up of Stone Patients with Idiopathic Hypercalciuria

Y. M. F. MARICKAR and G. ALAN ROSE

St Peter's Hospitals and Institute of Urology, London

Summary—One hundred and twenty-four male stone formers with idiopathic hypercalciuria were followed up for 4 to 27 years (mean 12.2). Twenty-eight received restricted calcium diet alone, 52 also received bendrofluazide, 11 cellulose phosphate, and 33 received mixtures of those drugs. Although urinary calcium values fell in all groups, the stone recurrence rate remained unacceptably high. Patients on cellulose phospate fared worst and this drug seems unsatisfactory as a sole agent. Urinary calcium was highest in patients without stone recurrences, but in patients with stone activity a higher stone recurrence rate was associated with higher urinary calcium and lower urinary volume.

Whether or not urinary calcium is raised in patients with calcium oxalate/phosphate urolithiasis without other clear metabolic cause is still a matter of controversy (Gill and Rose, 1985). Most workers consider it desirable to lower urinary calcium for the treatment of such urolithasis and various methods have been used: dietary manipulation (Rao *et al.*, 1982; Rose, 1982), thiazide diuretics (Yendt *et al.*, 1970; Rose and Harrison, 1974; Marickar *et al.*, 1985), cellulose phosphate (Dent *et al.*, 1964; Blacklock and Macleod, 1974; Pak *et al.*, 1974; Rose and Harrison, 1974), orthophosphate (Bernstein and Newton, 1966; Oliver *et al.*, 1974), bran (Shah *et al.*, 1980) and more recently flurbiprofen (Rao and Blacklock, 1983). While most of these methods lower urinary calcium, there is much less evidence that this lowering decreases the stone formation rate (Pak *et al.*, 1974; Backman *et al.*, 1979, 1980; Brocks *et al.*, 1981; Scholz *et al.*, 1982; Churchill and Taylor, 1985). It seemed appropriate to take advantage of a prolonged trial of various therapies at St Peter's Hospitals to compare the effects of reducing urinary calcium upon stone formation rate.

Patients and Methods

During the period of follow-up all patients were treated with a restricted calcium diet to which was added either bendrofluazide (5 mg/day) or cellulose phosphate (15 g/day) or both if the initial fall in urinary calcium was considered insufficient. After about 1975, dietary oxalate was also restricted in all cases. All patients were advised and repeatedly encouraged to aim at producing a 24-h urinary volume of at least 3 l. Measurements of the 24-h urinary volume and composition were made every few months. Plain X-ray films of the renal tract (KUB) were made at least annually. For this study only patients who had been followed up for at least 4 years were considered. These comprised 134 patients with a mean follow-up of 12.31 years. Ten were female and have not been included in this study. An attempt was made to divide the remainder into those with continuing stone formation and those who made no further stones, but we found this difficult even after careful examination of the clinical notes and X-rays. In fact it was necessary to recognise three groups of patients. In the first group were those in whom new stone formation had clearly taken place ("Red"). They were subdivided into those with stone activity in over 40% of

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Table 1 Mean (and SEM) 24-h Urinary Values Before and During Treatment

	Calcium (mmol)		*Oxalate (mmol)*		*Volume (l)*	
	Before	*During*	*Before*	*During*	*Before*	*During*
Diet only	10.2	8.3	0.32	0.31	2.3	2.6
Bendrofluazide	11.2	7.8	0.29	0.30	2.1	2.6
Cellulose phosphate	10.6	6.2	0.34	0.33	2.3	2.8
Mixed	12.0	7.9	0.40	0.40	2.4	2.6
Total	11.1 (0.27)	7.8 (0.18)	0.32 (0.02)	0.32 (0.01)	2.25 (0.08)	2.62 (0.06)

Table 2 Effect of Treatment on Stone Recurrence Rate

Treatment (No.)	*Definite Recurrence*	*Possible Recurrence*	*No Recurrence*
Diet (28)	11 (39.3%)	10 (35.7%)	7 (25.0%)
Bendrofluazide (52)	30 (57.7%)	14 (26.9%)	8 (15.4%)
Cellulose phosphate (11)	10 (90.9%)	1 (9.1%)	9 (0.0%)
Mixed (33)	21 (63.6%)	5 (15.2%)	7 (21.2%)
Total (124)	72 (58.1%)	30 (24.2%)	22 (17.7%)

follow-up years (Predominantly red) and the rest (Occasionally red). The second group comprised those in whom no further stone formation had occurred ("Green"), but in the third group it was not possible to say for certain whether or not new stone formation had occurred ("Yellow"). Some of these patients experienced symptoms of colic thought to be renal in origin, some had haematuria and/or passage of stones previously present. Even amongst the patients with definite new stone formation, there were periods when this definitely occurred ("Red years"), periods when no stone formation occurred ("Green years") and periods of uncertainty ("Yellow years").

After the clinical and radiological survey, urinary calcium, oxalate and volume were examined during the pre-treatment and on-treatment periods, the latter being broken down into red, yellow and green years. For each period of time, mean values were calculated and from these values, means were then calculated for the various groups of treatment.

Urinary calcium was measured by the standard flame atomic absorption spectrophotometric method. Urinary oxalate was measured during most of the period by the oxalate decarboxylase method of Hallson and Rose (1974), although this was changed to the automated oxalate oxidase method of Kasidas and Rose (1985) during the final follow-up year.

Results

At the beginning of the study 46 patients (37%) were under and the rest over 40 years of age; 55 (44%) had experienced a single stone episode and the result multiple episodes; 26 (21%) had had stone surgery, 64 (52%) had passed stones spontaneously, and 34 (27%) had both passed stones spontaneously and received surgery.

Twenty-eight patients were treated with diet alone, 52 with bendrofluazide alone, 11 with cellulose phosphate alone, and 33 with mixtures of these two drugs (Table 1). Patients who received diet alone had a lower mean initial urinary calcium value than the others because we gave drugs only to the more severe cases.

The stone recurrence rates with different therapies are shown in Table 2. Although the patients treated with diet only had the lowest recurrence rate, these were the mildest cases. Cellulose phosphate therapy was followed by a significantly higher stone recurrence rate than bendrofluazide and this is significant since there were no differences in pre-treatment measurements between these two groups of patients.

Table 3 shows a total of 1514 patient years of follow-up with 222 "red" years, 226 "yellow" and

Table 3 Status of Follow-up Years

Patient type and No.	*Red years*	*Yellow years*	*Green years*	*Total*
Red 72	222	161	525	908
Yellow 30	0	65	284	349
Green 22	0	0	257	257
Totals 124	222	226	1066	1514

Table 4 Mean (and SEM) 24-h Urinary Values in Patients With and Without Stone Recurrences

	Calcium (mmol)			*Oxalate (mmol)*			*Volume (l)*		
	Pre-	*During*	*P*	*Pre-*	*During*	*P*	*Pre-*	*During*	*P*
Predominantly red	12.0 (0.89)	8.2 (0.45)	<0.001	0.35 (0.06)	0.35 (0.02)	NS	2.29 (0.19)	2.67 (0.19)	NS
Occasionally red	10.7 (0.40)	7.4 (0.29)	<0.001	0.28 (0.03)	0.31 (0.01)	NS	2.13 (0.13)	2.64 (0.09)	NS
Yellow	10.0 (0.42)	7.5 (0.34)	<0.001	0.32 (0.03)	0.31 (0.02)	NS	2.45 (0.17)	2.56 (0.12)	NS
Green	11.3 (0.48)	8.5 (0.41)	<0.001	0.38 (0.07)	0.33 (0.02)	NS	2.28 (0.20)	2.60 (0.13)	NS

Table 5 Mean (and SEM) 24-h Urinary Values in Years with and without Stone Recurrence

	Calcium (mmol)	*Oxalate (mmol)*	*Volume (mmol)*
Red years	7.58	0.336	2.63
Green years	7.51	0.308	2.62

1066 "green" years, and it also shows how these years were divided between those patients with definite recurrences (red), those with no recurrences (green), and those in whom recurrences were doubtful (yellow).

Pre-treatment urinary calcium was highest in the patients with the worst recurrence rate, but this effect was small and not statistically significant (Table 4). There were no statistically significant differences in urinary volumes during treatment between the groups. Urinary oxalate was slightly higher during treatment in the predominantly red group than other groups but this did not show statistical significance.

The calcium and oxalate values were lower in the green than the red years but this did not achieve statistical significance (Table 5). Tables 6 to 8 show the urinary values split up into the red and green years in the red and green groups. Comparing urinary calcium in the predominantly and occasionally red groups, the value is always higher in the former ($P= <0.001$ in the red years and $P= <0.01$ in the green years). However, urinary calcium is even higher in the green years of the green group ($P= <0.001$ for occasional red group and not significant for predominantly red group).

Table 6 25-h Urinary Calcium (mmol) during Follow-up Years

Group	*Year type*	*Calcium*	*SD*	*N*
Predominantly red	Red	7.95	3.15	104
Predominantly red	Green	7.77	3.43	85
Occasionally red	red	7.07	2.84	77
Occasionally red	Green	7.13	2.63	333
Green	Green	8.26	2.55	203

Table 7 24-h Urinary Oxalate (mmol) during Follow-up Years

Group	*Year type*	*Oxalate*	*SD*	*N*
Predominantly red	Red	0.34	0.10	64
Predominantly red	Green	0.33	0.10	53
Occasionally red	Red	0.33	0.11	51
Occasionally red	Green	0.31	0.10	224
Green	Green	0.32	0.09	117

Table 8 shows that in the predominantly red group urinary volume was smaller in the red years than in the green years ($P= <0.001$).

Discussion

The main objectives in treating this group of stone formers were to decrease urinary calcium and to increase volume in the hope that stone formation rate would be reduced. There was a striking fall in overall urinary calcium from means of 11.1 to 7.8 mmol/24 h before and during treatment respectively, but the latter was still above normal (Gill and Rose, 1985). The 24-h urinary volume changed only slightly from 2.25 to 2.62 l, both of which are unusually high figures. It must be supposed that

Table 8 24-h Urinary Volume (l) during Follow-up Years

Group	*Year type*	*Volume*	*SD*	*N*
Predominantly red	Red	2.61	0.88	108
Predominantly red	Green	2.93	0.90	80
Occasionally red	Red	2.67	0.87	75
Occasionally red	Green	2.65	0.78	329
Green	Green	2.56	0.66	194

patients had already been advised during "pre-treatment" to increase water intake.

Table 2 shows that the overall stone recurrence rate over the mean period of 12.3 years was 58.1%, while only 17.7% were completely free from recurrence. No attempt has been made to compare the stone formation rates before and during treatment, but it is clear that the recurrence rate during treatment cannot be regarded as acceptable despite the reduced urinary calcium and high urinary volume.

The stone recurrence rate was lower in patients treated with diet alone (39.3%) than in patients treated with added drugs. This does not imply that the drugs were useless, since patients were selected for diet alone because of either few stone episodes or urinary calcium only slightly raised, or both.

Bendrofluazide was used more often than cellulose phosphate because of its lower cost and greater convenience. Some patients were given cellulose phosphate to gain experience or because they had a family history of gout or diabetes mellitus. No attempt was made to divide the patients into absorptive or renal types of hypercalciuria.

The worst stone recurrence rate of 90% was amongst those treated by cellulose phosphate and none of these patients was clearly free from recurrence during treatment (Table 2). There are several possible reasons for this. Cellulose phosphate lowers not only urinary calcium but also urinary magnesium (Dent *et al.*, 1964; Hallson *et al.*, 1981) and may raise urinary oxalate (Hallson *et al.*, 1976). An attempt was made to restrict the rise in urinary oxalate by warning the patients to avoid oxalate-rich foods. Table 1 shows that this was largely successful but no attempt was made to avoid a fall in urinary magnesium which was seen in these patients. Although cellulose phosphate lowers urinary calcium it should not be used as the sole drug.

Table 4 shows that it is difficult to identify a clear reason why some patients did well and some badly. While on treatment the "red" patients showed little difference in urinary calcium, oxalate or volume from "yellow" or "green" patients. However, the "red" patients were not continually making new stones; some had periods during which stone formation ceased and other periods during which they progressed and the urinary parameters may have varied at different times. The patients' years were therefore put into red, yellow and green categories and this is discussed further below. The 24-h out-patient urine collections might not have been representative of everyday urinary output, and there are some grounds for suspecting that this was so. Collections were often made at the weekend and some patients admitted that they could not maintain the same urine output during the week. Others increased water intake on the day of collection. In some cases, although the 24-h urine volume was high, the concentration of random out-patient sample of urine was also high and accompanied by crystalluria because some patients restricted water drinking to certain times of the day.

Although examination of the groups of patients showed no clear biochemical differences, such differences did become apparent on studying patient years (Tables 5-8). In Tables 6 and 7 urinary calcium and oxalate are seen to be lower in the green years than in the red years, although neither difference achieved statistical significance. Table 6 shows that although urinary calcium is higher in the green years of the green group than in the red years of the red group, within the red group alone urinary calcium was higher in those patients with the most stone activity.

It was concluded that in patients with stone activity and idiopathic hypercalciuria a lower urinary calcium was associated with less stone activity. However, lowering the urinary calcium should not be attempted with cellulose phosphate. However, in patients who do not make further urinary stones, the urinary calcium remainder higher than in those who did. Clearly there are other causes of stone formation than urinary calcium, and the evidence suggests that magnesium and oxalate may be such factors.

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The Authors

Y. M. F. Marickar, MB, BS, MS, MAS, Assistant Professor of Surgery, Medical College Hospital, Trivandrum, Southern India.

G. A. Rose, FRCPath, Consultant Chemical Pathologist.

Requests for reprints to: G. A. Rose, St Paul's Hospital, 24 Endell Street, London WC2H 9AE.

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Renal Stones in Children in Pakistan

S. A. RIZVI, S. A. NAQVI, Z. HUSSAIN and S. SHAHJEHAN

Department of Urology, Dow Medical College and Civil Hospital, and Department of Biochemistry, BMSI, Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Summary—One hundred and fifty children up to the age of 12 years with documented evidence of renal or ureteric stones were studied between July 1973 and June 1983.

The peak age group was between 10 and 12 years, the male to female ratio being 1.9:1. Abdominal pain was the commonest presenting symptom (66.6%). Asymptomatic stones or vague symptoms in 23 patients warrant a higher index of suspicion of renal stone disease in children. Thirty patients had associated renal insufficiency. One third of the children had a positive urine culture, *Proteus spp.* being the commonest organism. Congenital anomalies of the urinary tract were seen in 12% of patients. In the majority (59%), aetiological factors related to stone formation could not be identified.

One hundred and thirty patients underwent surgery for removal of stones. Analysis of calculi by X-ray diffraction and infrared spectroscopy revealed that stones were predominantly of mixed type, calcium oxalate being the commonest compound. The overall recurrence rate following surgical removal was 15%.

Calculus disease of the urinary tract is the commonest paediatric urological problem in Pakistan (Naqvi *et al.*, 1984a) and endemic vesical calculi are the predominant type (Rizvi, 1975). In the Department of Urology the number of patients with upper tract calculi has increased steadily over the last decade. It is too early to say whether this reflects any change in the pattern of paediatric urolithiasis, as has been observed in the industrial cities of some developing countries (Sutor, 1980). Moreover, upper tract stone disease in children assumes a greater clinical importance in view of the possibility of renal damage due to urinary obstruction and infection. This retrospective study was undertaken to review renal and ureteric stones in our paediatric patients in relation to clinical features, aetiological factors and stone composition.

Patients and Methods

Between July 1973 and June 1983, 945 children were admitted to the paediatric section of the Department of Urology; 680 (71.9%) had calculus disease of the urinary tract and the rest had upper tract calculi.

A detailed history and clinical examination were undertaken. Radiological investigations included plain film of the abdomen and intravenous urography. Ultrasonography, which became available in the latter half of the study, was performed if necessary. Physical, chemical and microscopic examination of the urine was followed by bacteriological study. A 24-h urine and serum specimen was analysed for calcium, phosphorus, uric acid, urea and creatinine and tubular reabsorbed phosphate (TRP) was calculated from the findings. Serum alkaline phosphatase was estimated in all cases. Serum cortisol and parathormone were estimated where indicated. Children with persistent alkaline urine underwent an ammonium chloride load test. Following surgical removal, the surface and central portions of calculi were analysed by X-ray diffraction crystallography (Sutor and Scheidt, 1968) and infrared spectroscopy (Tsay, 1961).

Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

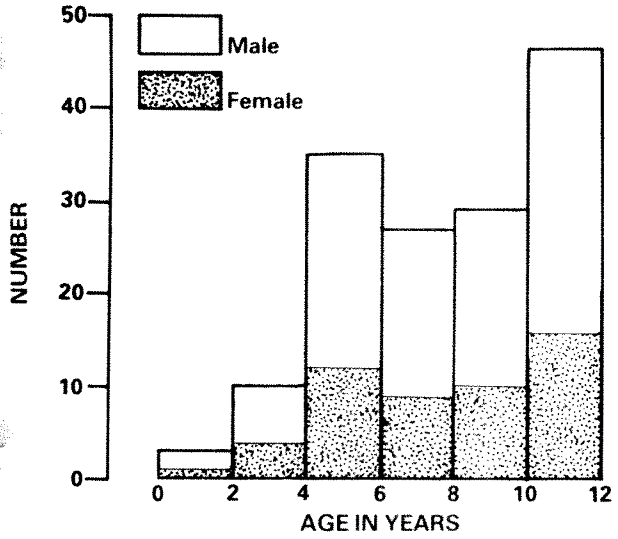

Fig. 1 Age and sex distribution.

Results

The series comprised 98 boys and 52 girls, ranging in age from 5 months to 12 years. The peak age group was between 10 and 12 years (Fig. 1). A positive family history of urolithiasis was found in 13 children (8.6%).

Abdominal pain was the principal presenting symptom in 100 children (Table 1), the duration of symptoms ranging from a few weeks to 7 years. The majority, however, did not complain of typical renal/ureteric colic and lacked lateralisation of pain. A history of macroscopic haematuria was reported in 53 children. Twenty-three had either asymptomatic stones or such vague symptoms that a diagnosis could be made only after detailed investigations. Seventeen patients were hypertensive on admission. In 12 the blood pressure returned to normal levels on follow-up.

Table 1 Clinical Presentation

	No. of cases (%)
Abdominal pain	100 (66.6)
Dysuria	69 (45.9)
Haematuria	53 (35.3)
Vague symptoms	23 (15.3)
Hypertension	17 (11.3)
Failure to thrive	10 (6.6)

Urinary tract infection was detected in 49 children (Fig. 2). In this group *Proteus mirabilis* was the commonest organism (41%). However, *Escherichia coli* was the commonest organism in female children, seen in 8 of 16 patients.

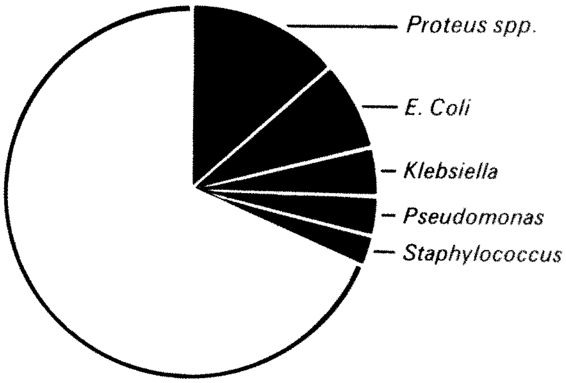

Fig. 2 Urinary pathogens.

One hundred and twenty-three children had renal and 20 had ureteric stones. Seven patients had stones in both the kidney and the ureter. Unilateral renal calculi were found in 100 children and 23 had bilateral renal stones. Of the children with ureteric calculi, three had bilateral stones.
stones.

On admission, 30 children had varying degrees of renal insufficiency associated with stone disease. The creatinine clearance in these cases ranged from 2 to 50 ml/min. In 9 cases correction of fluid and electrolytes and eradication of urinary tract infection restored the renal function to normal. Twenty-one children required dialysis prior to surgery. Post-operative dialysis was indicated in six children, three of whom were on dialysis at the conclusion of the study.

One hundred and thirty children underwent surgery. Six were considered unfit for and seven refused surgery. Seven children with ureteric stones passed them spontaneously. One hundred and ninety-five surgical procedures (ranging from 1-4 per child) were performed on 130 patients. The commonest procedure was pyelolithotomy (81 children) followed by ureterolithotomy (19 children). Nephrectomy was undertaken in five children. One child died of septicaemia on the third post-operative day. Two children with renal failure died 1 month and 6 months after surgery.

Aetiological factors relating to stone formation were found in 61 children (Table 2). Congenital anomalies of the urinary tract were detected in 18. The commonest malformation was obstruction of the pelviureteric junction (8 cases). Metabolic causes predisposing to stone formation were detected in 13 children (Table 2). Four patients

Table 2 Aetiological Factors

	No. of Cases (%)
Anatomical	
PUJ obstruction	8 (5.5)
Anomalies of fusion and rotation	5 (3.3)
Ureteric stricture	2 (1.3)
Ureterocele	3 (1.9)
Metabolic	
Hyperparathyroidism	2 (1.3)
Renal tubular acidosis	3 (1.9)
Hypercortisonism	2 (1.3)
Hypervitaminosis D	2 (1.3)
Immobilisation	4 (2.6)
Infective	30 (19.9)
Idiopathic	89 (59.3)
	150 (100.0)

were immobilised for periods ranging from 6 months to 1 year. Three children had Type 1 renal tubular acidosis and two had hyperparathyroidism.

One hundred stones were analysed either by X-ray crystallography or infrared spectroscopy. Most stones (78%) were a mixture of two or more compounds (Table 3). Calcium oxalate was the commonest compound, occurring as a surface constituent in 85% and in the central portion in 90%. Compounds of phosphate occurred more often on the surface (50%) than in the central portion (30%). In contrast, uric acid occurred in 40% in the central portion and in only 5% as a surface constituent.

Table 3 Stone Analysis of 100 Cases by X-Ray Diffraction and IR-Spectroscopy

	Surface	*Centre*
Ca. oxalate (whewellite/weddelite)	45	30
Ca. phosphate (apatite/brushite/struvite)	15	—
Uric acid (anhydrous/dihydrate)	—	10
Oxalate + uric acid	5	30
Phosphate + oxalate	35	30

Oxalate : surface 85%, centre 90%
Phosphate: surface 50%, centre 30%
Uric acid : surface 5%, centre 40%

The overall recurrence rate following surgery was 13%. Six children had retained calculi. On follow-up, 10 children showed a recurrence. In three cases recurrence appeared to be the result of failure to eradicate *Proteus spp.* infection. Follow-up ranged from 3 months to 7 years and 27 children were lost to follow-up.

Discussion

Analysis of data showed that most children were aged between 6 and 12 years, the peak falling between 10 and 12 years. In contrast, lower tract calculi afflicted much younger children, the peak being between 2 and 4 years (Naqvi *et al.*, 1984a). The male to female ratio in children with upper tract calculi was 1.9:1 as against 10:1 in the case of endemic bladder stones. This again suggests that the two types of urolithiasis are likely to be different clinical entities. Moreover, the primary physician has a poor index of clinical suspicion because of the endemic nature of lower tract calculi in children in Pakistan. Thus there is a considerable delay in referral of upper tract calculi, as is evident from the poor renal function noted in one fifth of cases. The prevalence of unscientific methods and the fear of surgery may be other factors contributing to the delay in seeking treatment (Singh *et al.*, 1980, 1982).

Stone analysis by contemporary methods revealed that pure calculi were seen in 22% of samples. Most stones were of mixed composition (78%), which points to a multiplicity of environmental factors. Calcium oxalate was the commonest component, seen as a surface constituent in 85% and in the centre in 90%. This is in agreement with findings reported in Turkish and Indian children (Sutor, 1980). Studies on children in Europe and North America have shown a preponderance of phosphate in upper tract calculi (Farrell and Marshall, 1974; Hodgkinson, 1977), whereas phosphate was present in one-third of the central portion in the present study. The incidence of phosphate was, however, higher than in bladder stones reported from Pakistan (Naqvi *et al.*, 1984b), which may be related to *Proteus* infection in many cases. The occurrence of uric acid in the centre in 40% of stones and on the surface in only 5% indicates that greater attention should be paid to the possibility of crystallisation of urates as a prime event in calculogenesis.

The predisposing factors relating to stone disease could be identified in only 40% of patients. Series from the Western world have reported identification of aetiological factors in 25 to 87% of children (Daeschner *et al.*, 1960; Churchill *et al.*, 1980). Infection stones were the largest single group in the present series (20%). This may be an expression of the fact that infection with urea-splitting organisms was the predominant type in the present study.

Our experience with dialysis in children suffering from renal insufficiency has been encouraging, since they responded reasonably well to surgery. Similar findings have been reported from India by Gupta *et al.* (1985). In 80% of children treated by surgery, the removal of obstruction and eradication of infection contributed to the restoration of adequate renal function.

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The Authors

S. A. Rizvi, FRCS, FRCSE, Professor of Urology.

S. A. Naqvi, MCPS, MS(Urology), Senior Registrar, Department of Urology.

Z. Hussain, MCPS(Surgery), Senior Registrar, Department of Urology.

S. Shahjehan, MBBS, M.Phil(Biochemistry), Assistant Professor, Department of Biochemistry.

Requests for reprints to: S. A. Rizvi, Department of Urology, Dow Medical College and Civil Hospital, Karachi, Pakistan.

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Pressure Changes in the Dilated Upper Urinary Tract on Perfusion at Varying Flow Rates

E. W. LUPTON, D. HOLDEN, N. J. R. GEORGE, R. J. BARNARD and D. RICKARDS

Departments of Urology and Radiology, University Hospital of South Manchester, Manchester

Summary—The conventional Whitaker test assesses the pressure response to a constant perfusion rate of 10 ml/min. Twenty-eight kidneys were perfused at increasing flow rates up to 20 ml/min. Nine became obstructed at rates of 12 to 20 ml/min. The feasibility of such a high urine output has been tested and confirmed. The standard Whitaker test may therefore miss some cases with potentially obstructive hydronephrosis, the effects of which may be deleterious to renal function.

Since its inception in the early 1970s, pressure flow analysis of the upper urinary tract has been criticised for its invasive, non-physiological nature. Nevertheless, many centres find it a useful test. In the original description of the test the kidney was perfused at a constant rate of 10 ml/min (Whitaker, 1979). Observations made during diuresis renography and urography, however, have indicated that urine flow rates from some kidneys may exceed 10 ml/min during an intense diuresis. It is possible that discrepancies in results obtained during renographic and perfusion studies might be explained on a basis of the differing flow rates attained during the test procedures. This study was designed to determine the maximum urine output which may result from physiological or non-invasive stimuli in normal control subjects and to assess the relative renal pelvic pressure response of the dilated upper tract to high infusion rates (if necessary above 10 ml/min) during pressure flow testing.

Patients and Methods

Sixteen control subjects with normal upper urinary tracts consented to fluid loading tests. Eleven volunteers received frusemide 0.5 mg/kg following either intravenous (mean 2.0 litres) or oral (500 ml) fluid loads. Five persons received no intravenous diuretic agent but drank beer steadily at a rate of 500 ml per h.

Twenty-eight kidneys in 27 patients (age range 16-66 years, mean 36) with urographically demonstrated upper tract dilatation were assessed by antegrade pressure flow studies. In 22 patients the dilatation was confined to the renal pelvis but six also had dilated ureters. All patients had previously undergone diuresis renography using standard techniques (O'Reilly *et al.*, 1979). A conventional Whitaker test was carried out by percutaneous transparenchymal needle puncture of the affected kidney under X-ray or ultrasound control. Pressure measurements were combined in all cases with antegrade pyelography. The equipment for these studies is now well established. Perfusion of fluids at high rates was produced by two Braun-Melsungen syringe pumps arranged in parallel. The remaining equipment included three-way taps connecting the renal pelvic catheter by manometer tubing to the syringes and Statham transducers.

The usual criteria were used to denote obstruction, namely 22 cm H_2O obstructive; 15 to 22 cm H_2O equivocal; 15 cm H_2O non-obstructive (Whitaker, 1979). If perfusion at 10 ml/min resulted in a sustained high renal pelvic pressure, the test was stopped. If, however, the pressure remained low on perfusing at this rate for a reasonable length of time (usually 20/30 min to ensure complete filling of the system), the perfusion rate was increased to

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Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

12 ml/min. If there was no pressure rise at this rate the flow was increased again to 14 ml/min, then 17.5 ml/min and finally 20 ml/min. If a significant pressure rise above 22 cm H_2O occurred at any given flow rate the study was terminated without proceeding to higher levels.

Results

The maximum total flow rates obtained in the volunteers are recorded in Table 1. It is notable that the subjects given frusemide had mean total urine flow rates in excess of 30 ml/min. At least one of their kidneys must therefore have been producing urine at a maximum rate of more than 10 ml/min.

Table 1 Maximum Urine Flow Rate (ml/min) in 16 Volunteers

Frusemide + iv fluids	(5)	13-50	(mean 30)
Frusemide + oral fluids	(6)	21-50	(mean 32)
Beer	(5)	11-20	(mean 17)

The results of the pressure/flow studies in the kidneys with upper urinary tract dilatation are shown in Table 2. Fourteen kidneys were obstructed at a flow rate of 10 ml/min. In a further nine cases, however, the relative renal pelvic pressure was greater than 22 cm H_2O on perfusing at rates of 12 to 20 ml/min. Obstruction would have been excluded in these patients using conventional Whitaker criteria. The results of diuresis renography and the subsequent management of these cases are shown in Table 3.

Table 2 Pressure/flow Studies in 28 Kidneys with Upper Tract Dilatation. (Perfusion Rate 10-20 ml/min)

		No.
Obstructed	10 ml/min	14
	12 ml/min	1
	14 ml/min	1
	17.5 ml/min	5
	20 ml/min	2
Non-obstructed		5

The potential effects of such a high flow rate obstruction are illustrated by the following case report.

A 35-year-old woman with right idiopathic hydronephrosis complained of mild loin pain. Diuresis renography demonstrated 50% relative function in the right kidney but an obstructive excretory pattern. A pressure/flow study showed a sustained relative renal pelvic pressure of 23 cm H_2O while perfusing at 17.5 ml/min but normal pressure with lower flow rates. A conservative follow-up was instituted but renography 3 months later showed a drop in the function of the affected kidney to 14%. Pyeloplasty was performed without delay and 5 months later the function returned to 54%.

Table 3 Results of Diuresis Renography and Subsequent Treatment

Kidneys (9) obstructed at flow rates 12-20 ml/min		
Diuresis renogram	Obstructed	5
	Non-obstructed	1
	Equivocal	1
	Poor function	2
Treatment	Surgery	7
	Conservative	2

Discussion

The work of Whitaker has made a significant contribution to the understanding of the dynamic component of upper urinary tract dilatation. The Whitaker test, however, has been subjected to criticism (Ripley and Somerville, 1982; Djurhuus *et al.*, 1985). The fixed flow rate of 10 ml/min was an arbitrarily chosen figure which, as our study of normal volunteers has shown, does not necessarily represent the maximum potentially achievable flow rate for a kidney during a physiological diuresis. Pfister *et al.* (1982) have advanced the hypothesis that equivocal pressures in perfusion studies at rates of 10 ml/min require assessment at higher flow rates to ensure that latent obstruction is not overlooked.

The present study of 28 obstructed upper tracts has demonstrated nine kidneys (32%) with obstructive pressure rises only in response to flow rates above 10 ml/min. In two of these cases longstanding decompensation of the pelvicaliceal system associated with poor renal function may explain the obstructive pressure rise occurring only at high perfusion rates. It is interesting that five of the nine cases had obstructive diuresis renograms, supporting the contention that the diuretic stimulus during renography resulted in a urine output exceeding 10 ml/min from the affected kidney. It might further be postulated that in the remaining four kidneys the flow rate induced by frusemide was less than that attained during the pressure/flow studies.

Each renal pelvis and ureter probably has a maximum acceptable flow rate before a pressure rise occurs. The volunteer study has indicated that it is not difficult to achieve flow rates of 20 ml/min per kidney. If this occurs frequently in a hydronephrotic kidney regular intermittent obstruction may result. Such a situation could well have caused the deterioration in renal function observed in the case report patient (see above).

It remains debatable how often in practice a urine output greater than 10 ml/min/kidney is produced. However, some patients—notably the young beer drinker and the older subject on diuretic medication—may attain such high flow rates and experience loin pain associated with intermittent obstruction.

In conclusion, the conventional Whitaker test fails to identify some cases of potentially high pressure hydronephrosis. Furthermore, flow rates in excess of 10 ml/min/kidney are achievable in certain physiological situations.

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The Authors

E. W. Lupton, MD, FRCS, Consultant Urologist.
D. Holden, FRCS, Research Fellow in Urology.
N. J. R. George, FRCS, Lecturer in Urology.
R. J. Barnard, FRCS, Consultant Urologist.
D. Rickards, FRCS, formerly Consultant Radiologist, University Hospital of South Manchester. Now Consultant Radiologist, Middlesex Hospital, London.

Requests for reprints to: E. W. Lupton, Department of Urology, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR.

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The Importance of Recognising Renal Oncocytomas

W. T. LAWRENCE and N. M. S. BAJALLAN

Departments of Urology and Pathology, Norfolk and Norwich Hospital, Norwich

Summary—Oncocytomas of the kidney are infrequently reported tumours. They have distinct clinical and pathological features, but most cases have been discovered retrospectively. Nine series have been analysed (including four cases in Norwich) to define the features of these tumours. One of our cases is noteworthy because it is the largest individually reported tumour of this type and it contained a large cyst.

Oncocytomas are benign and have an excellent prognosis. Failure to identify this subgroup may bias the perceived effectiveness of treatment for renal carcinoma.

Oncocytes are large epithelial cells with finely granular eosinophilic cytoplasm. Hamperl (1962) coined the term "oncocyte" by hybridising the Greek words "Onkousthai" (to swell) and "Cyte" (a cell) to convey this increase in cell volume and he regarded this oncocytic transformation as a degenerative metaplasia, whereas Tremblay (1969) considered it to be an expression of mitochondrial disease. Oncocytic tumours have been described in many organs. Oncocytomas of the kidney are infrequently reported neoplasms. They have distinct clinical and pathological features which distinguish them from renal carcinomas and were first reported by Zippel in 1942. Only six cases were documented in the world literature until 1976, when Klein and Valensi published a study of 13 cases. During the past 9 years several series and many individual cases have been reported. Most have been discovered by retrospective analysis of previously diagnosed renal carcinomas.

Patients and Methods

Eight reports on renal oncocytomas during the period 1976 to 1984 have been analysed, together with a series from Norwich. A total of 166 oncocytomas were diagnosed but only 12 were found prospectively. The remaining 154 cases were discovered by retrospective analysis of renal carcinoma cases. The number of neoplasms included for this study was 4409 (Table 1).

Definition

Oncocytomas are composed entirely of oncocytes which have finely granular eosinophilic cytoplasm and are often arranged in an organoid pattern of cell nests. Although focal nuclear pleomorphism may be present, mitotic figures and necrosis are absent. A few of the cases studied were evaluated by electron microscopy. Ultrastructurally, oncocytes showed a striking number of mitochondria but otherwise scanty cellular organelles (Klein and Valensi, 1976; Merino and Livosi, 1982).

Results

Analysis of the nine retrospective series shown in Table 1 gives an incidence of 3.8% for oncocytomas when compared with renal carcinomas. The range was 3.1 to 6.6% (Klein and Valensi, 1976).

The following features were assessed for as many of the 166 cases as information from the original articles allowed: age and sex of the patient; side and site of the tumour; presenting features; presence or absence of pain and haematuria; size of the lesion; macroscopic and microscopic features and subsequent follow-up (Table 2). There were 113 (68%)

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985.

Table 1 Analysis of Retrospective Studies to Determine the Incidence of Oncocytomas

Year	*Author*	*Years studied*	*No. of cases*	
1976	Klein and Valensi	1952-1975	4 + 9/ 198	6.6%
1979	Ejeckam *et al.*	Not known	3 + 5/ 185	4.3%
1980	Yu *et al.*	1963-1977	5/ 107	4.7%
1981	Lieber *et al.*	1950-1979	90/2797	3.2%
1982	Merino and Livolsi	1958-1979	14/ 263	5.3%
1983	Fairchild *et al.*	1954-1982	4 + 7/ 219	5.0%
1983	Barnes and Beckman	1947-1981	10/ 257	3.9%
1984	Maatman *et al.*	1968-1983	11/ 254	4.3%
1985	Lawrence and Bajallan	1974-1984	1 + 3/ 129	3.1%
			12 + 154/4409	3.8%

Twelve cases were diagnosed prospectively. The remaining 154 cases were discovered by retrospective analysis of cases previously diagnosed as renal cell carcinoma.

Table 2 Analysis of Oncocytomas from Retrospective Studies

Men	113	68%	(n = 166)
Women	53	32%	(n = 166)
Age range	29 —	84 yrs	
Age mean		62 yrs	(n = 155)
Left side tumour	66	50%	(n = 132)
Right side tumour	66	50%	(n = 132)
Size range	2.5 —	26 cm	(n = 155)
Size mean		7.6 cm	(n = 133)
Incidental presentation	114	69%	(n = 166)
Symptomatic presentation	52	31%*	(n = 166)

Symptoms included:
Flank pain: Palpable mass; Frank haematuria.
Hypertension was found in some patients.
* This contrasts with a figure of 80% for renal cell carcinomas.

men and 53 (32%) women. The patients ranged in age from 29 to 84 years (mean 62). There were 66 (50%) right-sided and 66 (50%) left-sided tumours. One bilateral case was also reported (Maatman *et al.*, 1984). The neoplasms were evenly distributed between the upper pole, lower pole and midportion of the kidney and ranged in size from 2.5 to 26 cm. The mean diameter was 7.6 cm.

One hundred and fourteen tumours (69%) were discovered incidentally during diagnostic evaluation of complaints unrelated to the kidney. Only 52 (31%) had one or more of the classical triad of symptoms associated with renal carcinomas, namely haematuria, loin pain and a palpable mass. Hypertension was recorded in 39 of 147 (26%) cases.

This Series

In September 1982 a 69-year-old male patient presented with generalised pruritus. Clinical exami-

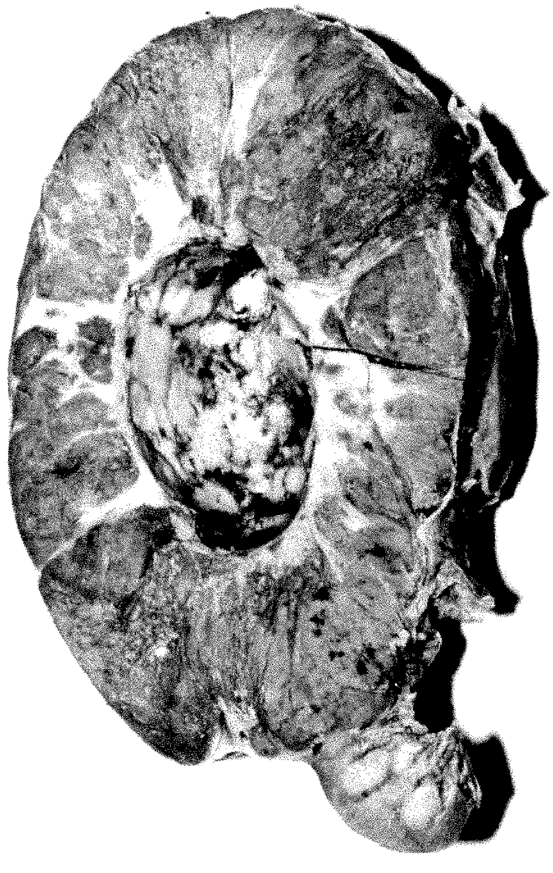

Fig. 1 Macroscopic pathology from case 1 illustrating the appearance of a renal oncocytoma. The margins of the tumour are well defined and only a small piece of the lower pole can be seen. This case shows a large central cyst with radiating scar tissue.

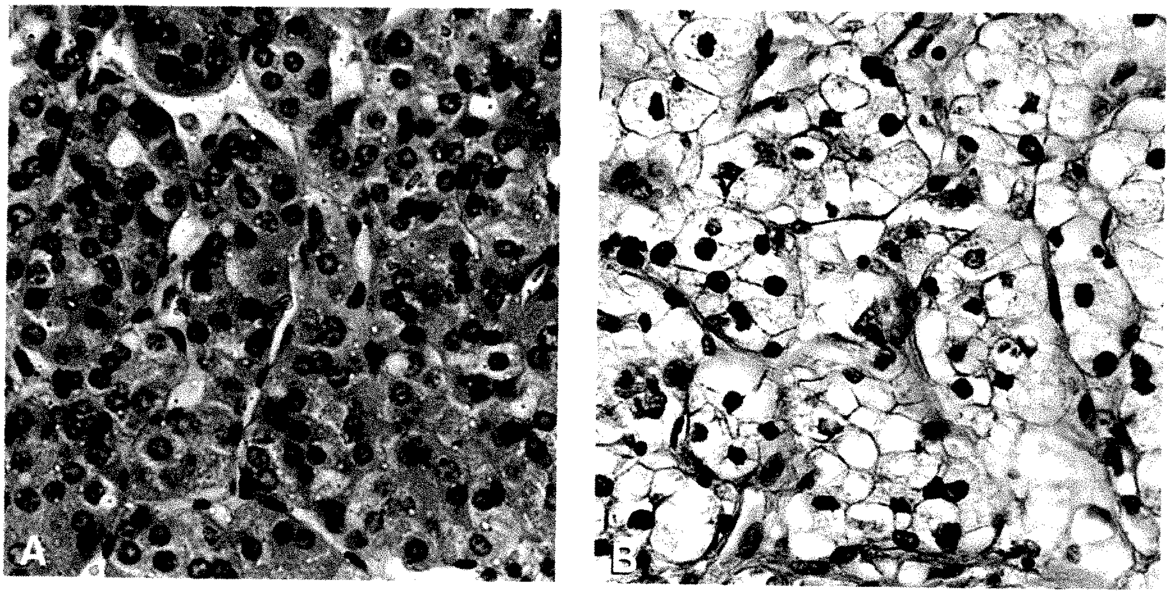

Fig. 2 Microscopic pathology of oncocytoma showing uniform eosinophilic cells (A), contrasting with clear cells and pleomorphic nuclei of renal carcinoma (B). (H and E × 400).

Table 3 Age, Sex Distribution, Clinical and Pathological Features of four Renal Oncocytomas from Norwich

Patient	*Age*	*Sex*	*Presenting symptom*	*Associated clinical findings*	*Gross pathological findings*	*Year of presentation*	*Outcome*
1	69	M	Pruritus	Left loin mass	19 × 18 × 11 cm tumour L. kidney, tan colour, central cyst	1982	3 years Well
2	73	F	Haematuria Clot colic	Hypertension	3.5 cm tumour L. kidney	1976	9 years Well
3	50	M	Abdominal colic Constipation	Sigmoid colectomy Diverticular disease	16 × 13 × 13 cm tumour L. kidney	1979	6½ years Well
4	73	M	Haematuria Dysuria	Transitional cell Bladder tumour	5.5 cm tumour L. kidney, central scar	1984	1 year Well

nation revealed a large mass in the left hypochondrium. Further investigation confirmed the presence of a renal tumour. A left radical nephrectomy was performed. Pathological examination showed a 19 × 18 × 11 cm tumour (Fig. 1) which was not a renal carcinoma but a renal oncocytoma (Fig. 2). This was the first such tumour recorded in Norwich and prompted a retrospective evaluation of 129 cases diagnosed as renal carcinoma. This 10-year pathological review (by NMSB) yielded a further three cases (Table 3).

Discussion

Until the last decade, renal oncocytomas were largely unrecognised. Their five main features were categorised by Yu *et al.* (1980).

Most patients are asymptomatic and the tumours are found incidentally; consequently they may become very large. Symptoms, if present, are similar to those of renal carcinoma. Oncocytomas are well circumscribed and often have a uniform tan colour. Necrosis is absent and haemorrhage rare. A central stellate scar has been recorded by many observers. Histologically they are composed of diffuse and organoid nests and cords of oncocytes without mitotic activity (Fig. 2). Oncocytes show abundant mitochondria but otherwise few cellular organelles. Histochemical analysis shows a high level of ATP-ase and oxidative enzyme

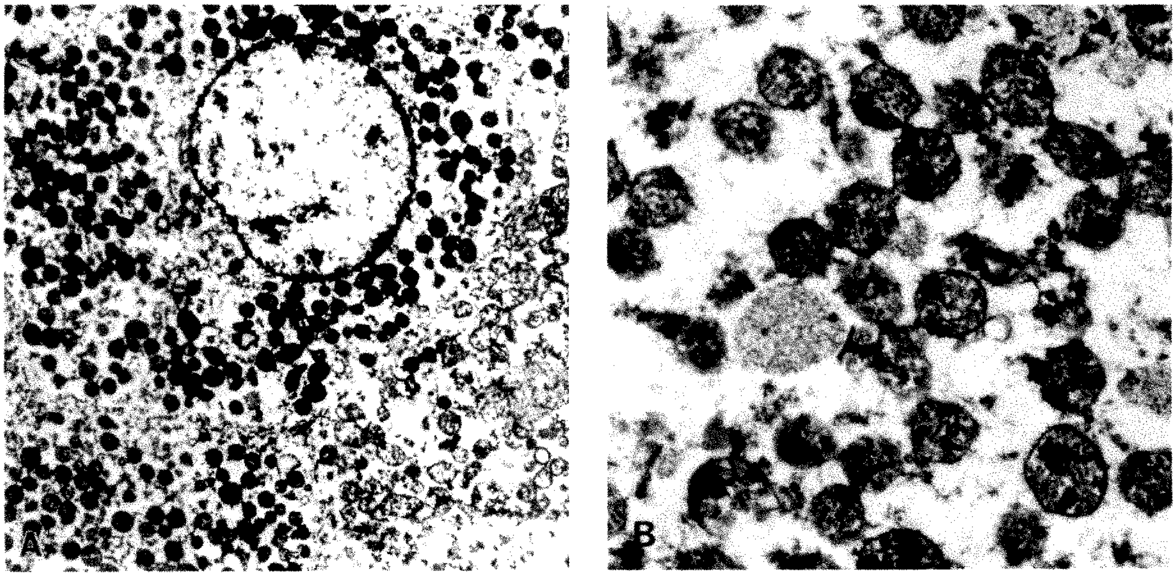

Fig. 3 Electronmicrograph illustrating (A) polyhedral cells with round to oval centrally located nuclei (× 4800). (B) The cytoplasm is packed with mitochondria (× 35,200).

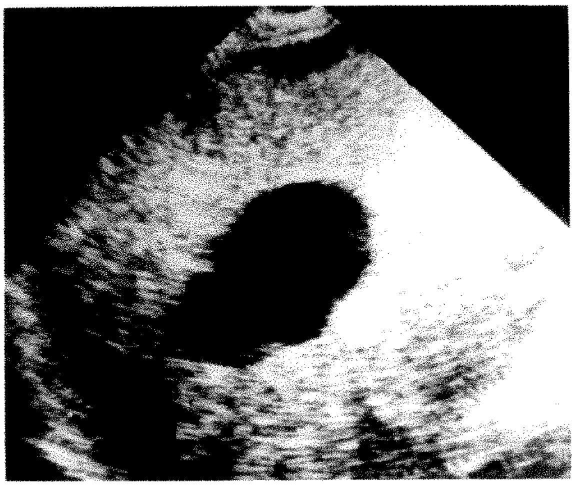

Fig. 4 Ultrasound scan of left renal oncocytoma with central cyst. (Patient 1)

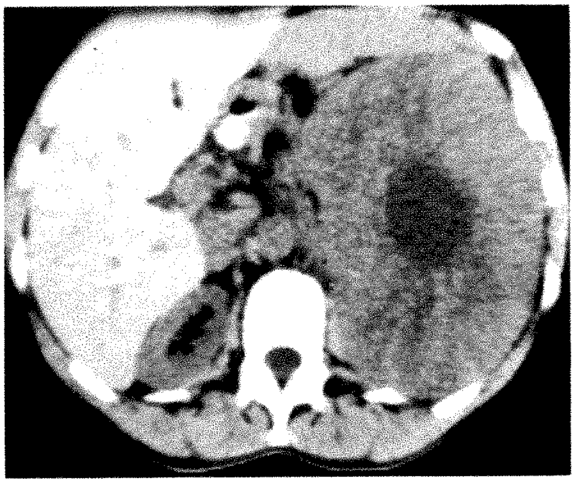

Fig. 5 CAT scan of patient 1 showing the very large oncocytoma compared with a normal right kidney. The central cyst is visible.

activity (Fig. 3). Despite their large size, these tumours are benign and have an excellent prognosis.

Analysis of the retrospective studies (Table 1) may be compromised in several ways. In the study from the Mayo Clinic (Lieber *et al.*, 1981) only patients identified as having well differentiated granular or dark cell carcinomas were selected for study. The remaining 8 series included all cases of renal carcinoma. Inadequate tumour sampling may confuse the diagnosis as many renal cell carcinomas have areas of cells with "oncocytic" features. It is for this reason that preoperative aspiration cytology or frozen section examination may be misleading (Barnes and Beckman, 1983). Oncocytomas behave as "benign" tumours and only 4/166 (2.4%) cases developed distant metastases. Further sampling of these more aggressive neoplasms may have shown other histological elements characteristic of renal carcinomas.

Recently a few cases of "malignant" oncocytoma have been reported. It is unclear at the present time if this represents a true spectrum of disease or if sampling may have caused diagnostic error. Klein and Valensi (1976) suggested using the term Proximal Tubular Adenoma as an alternative to Oncocytoma as their evidence concluded oncocytes were derived from proximal tubular epithelium. A recent study (Eble and Hull, 1984) has questioned this original finding by supporting a distal tubular origin for these cells.

The importance of recognizing oncocytomas is that they are benign in nature and have an excellent prognosis. Furthermore, failure to identify this subgroup may bias the perceived effectiveness of treatment for renal carcinoma.

The first Norwich case (patient 1) is noteworthy on two counts. It is the first reported case of an oncocytoma with a large central cyst (Fig. 1). Ultrasound and CAT scans demonstrated the well defined margin of the tumour and the central cystic region (Figs 4 and 5). Secondly, this tumour represents the largest individually reported case.

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The Authors

W. T. Lawrence, FRCS, formerly Registrar in Urology, Norfolk and Norwich Hospital. Now Senior Registrar, Department of Urology, University and City Hospitals, Nottingham.

N. M. S. Bajallan, MB, ChB, formerly Senior Registrar in Histopathology, Norfolk and Norwich Hospital. Now Senior Registrar, Department of Histopathology, Addenbrooke's Hospital, Cambridge.

Requests for reprints to: W. T. Lawrence, Department of Urology, City Hospital, Hucknall Road, Nottingham.

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The Effects of Double J Stenting on Unobstructed Ureters

An Experimental and Clinical Study*

J. W. A. RAMSAY, S. R. PAYNE, P. T. GOSLING, H. N. WHITFIELD, J. E. A. WICKHAM and D. A. LEVISON

Departments of Urology and Pathology, St Bartholomew's Hospital; Academic Unit, Institute of Urology, London

Summary—Upper tract pressure flow studies in four clinically unobstructed ureters with double J stents *in situ* indicated that urinary flow occurred mainly around the stent and that there was significant vesicorenal pressure transmission. This study examined the dynamics of ureteric urinary flow and morphological effects consequent upon stenting a ureter *in vivo*. In a porcine model, ureteric intubation caused a rise in intrapelvic pressures, hydroureter, vesicorenal reflux and generalised thickening of the ureteric wall with characteristic histological changes in the urothelium. These findings suggest that double J stents may compromise urinary drainage when ureteric obstruction is not present, urging caution in their use in the damaged, unobstructed upper urinary tract.

The practice of urinary diversion using double J stents is well established in the treatment of upper urinary tract obstruction (Hepperlen *et al.*, 1978), but the post-operative use of splints has remained a controversial issue (Smith and Butler, 1976). The rationale for using double J stents followng upper tract surgery or trauma depends upon their ability to effect urinary diversion whilst causing minimal functional or morphological disruption. Urine has, however, been seen to flow around ureteric endoprostheses (Ramsay and Whitfield, 1985), which implies that either these stents cannot accommodate a normal urine flow or that they cause a dilatation of the ureter around the stent due to some cytotoxic effect (Drake *et al.*, 1962). This study was designed to determine whether double J stents can transport physiological urine flows and whether these catheters intefere with upper tract dynamics.

Materials and Methods

This study was in three parts. First, an *in vitro* model was constructed to determine the optimal flow capabilities of double J stents; second, a porcine model was adopted to determine *in vivo* the effects of these stents on upper tract pressures; third, a clinical study was made of their effects on renal dynamics following upper tract surgery.

The maximal flow capacity of double J stents was measured in an *in vitro* model consisting of a pressure vessel perfused at a known rate by a syringe pump, fluid being able to escape only via a stent mounted in the rig. The vessel was filled with water at room temperature and the pressure within it measured via a fluid-filled line connected to a Bell and Howell 4327I external transducer. Pressures generated by known fluid flow rates through the system were determined in 5, 6 and 7 F polyurethane and silicone stents at perfusion rates between 1 and 10 ml/min.

The effects of ureteric intubation on upper tract pressures in a porcine model were investigated by intubation of one ureter with a 5 or 6 F polyurethane double J stent for 1 week and for 3 weeks. The results were compared with those from a control group of animals with unstented ureters. The intrarenal pressures were measured using either a Miller CR10 catheter-mounted sensor or by connection to an external Bell and Howell transducer. Perfusion of this system was by a diuresis of 3 ml/min. Bladder pressure was measured synchronously and recordings were made of the intrarenal pressures before and after diuresis and following emptying and filling of the bladder. Morphological and histological changes in the intubated ureter were noted and compared with control data obtained from the normal ureter of the same animal.

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* Awarded the Eschmann Prize for the best poster at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Four patients who had undergone ureteric surgery (1 dismembered pyeloplasty, 1 percutaneous pyelolysis and 2 complicated ureterolithotomies) were managed with operative insertion of a 7 F double J stent and ipsilateral nephrostomy drainage because there was urinary extravasation at the completion of the operative procedure. Each of these patients was investigated 1 week later by antegrade flow perfusion studies.

Results

The *in vitro* study demonstrated that 5, 6 and 7 F stents were capable of transmitting 10 ml fluid/min with minimal pressure rise (Table). Fluid can, therefore, be transmitted through these stents with a clinically undetectable pressure rise at physiological flow rates of up to 4 ml/min (Fig. 1).

Urine flow was seen to occur around the stented ureter in the porcine model (Fig. 2), the ureter

Table Pressures generated in the *in vitro* model during fluid perfusion of representative polyurethane 5 and 6 F double J stents and a 7 F silicone stent

Flow rate (ml/min)	*Pressures generated (cm H_2O)*		
	5 F	*6 F*	*7 F*
1	0.23	0.07	0.13
2	0.57	0.15	0.33
3	0.80	0.25	0.50
4	1.33	0.36	0.70
5	1.75	0.50	0.93
6	2.13	0.62	1.13
7	2.65	0.80	1.43
8	3.15	0.95	1.73
9	3.73	1.05	2.00
10	4.40	1.30	2.30

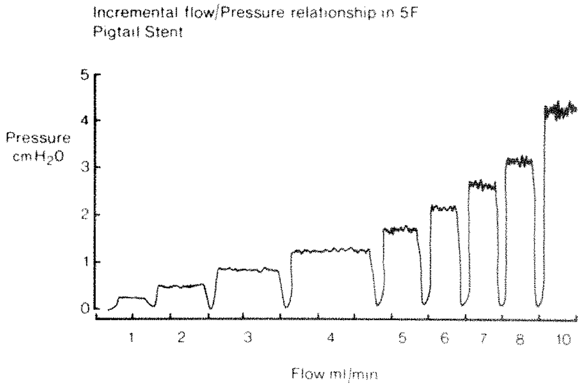


Fig. 1 Example of increase in pressure required to produce a fluid throughput of 1 to 10 ml/min through 5 F polyurethane double J stent.

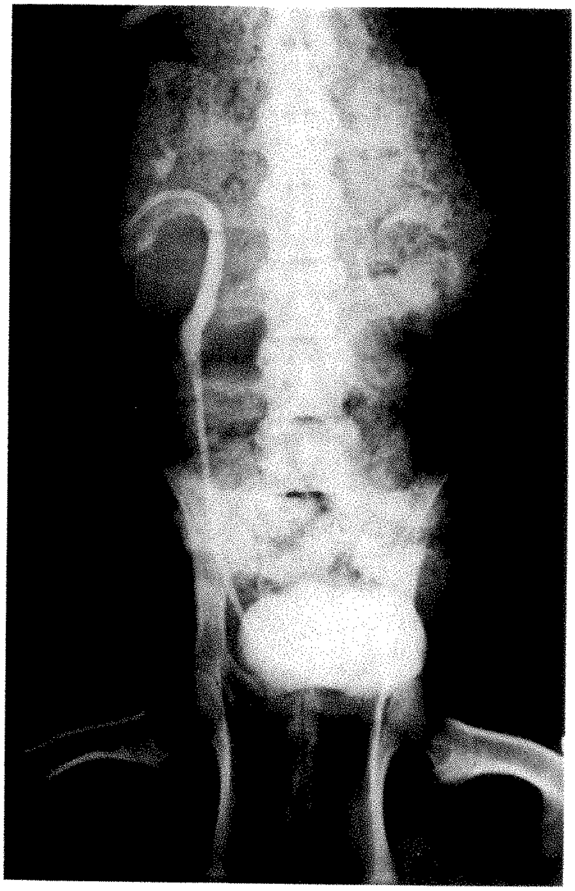


Fig. 2 Intravenous urogram at 15 min showing contrast flowing around a double J stent inserted 3 weeks previously.

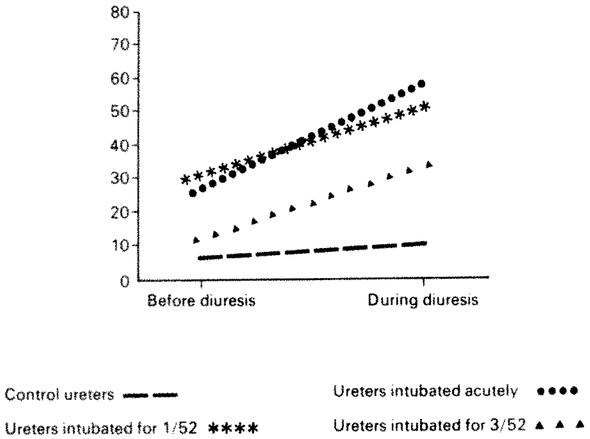


Fig. 3 Graph showing the intrarenal pressures acutely at 1 week and 3 weeks after intubation and comparison with normal controls before and during diuersis.

being macroscopically dilated even after intubation for 1 week with copious mucus production and in the absence of infection. Studies showed an increase in baseline pre-perfusion intrarenal pressures following acute and chronic intubation when compared with controls, this difference being most marked during diuresis. Also, the temporal length of intubation decreases the intrarenal pressure generated during diuresis, pressures being highest in the acutely intubated group (Fig. 3). These changes were size-dependent. Drainage of the bladder during diuresis also caused a reduction in intrarenal pressure (Fig. 4), implying that intravesical pressure was directly transmitted to the upper tract under these conditions. Histologically the intubated ureters showed a constant and generalised thickening of the wall and degeneration of the epithelium with vacuolation of cells, patchy atrophy and hyperplasia of the epithelium.

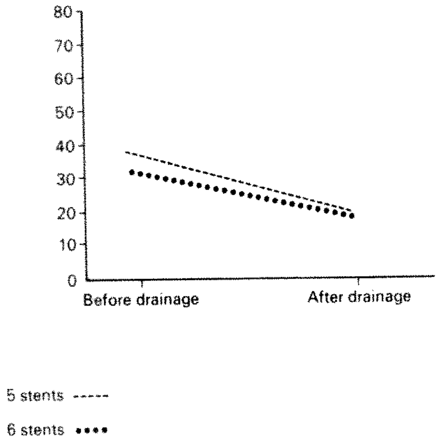


Fig. 4 Effect of bladder drainage on intrarenal pressure during diuresis.

Radiological evidence of ureteric dilatation was present in each of the clinical cases at 1 week, flow occurring around the stent with and without antegrade perfusion. Pressure flow studies did, however, show an equivocal result with differential pressure rises up to 16 cm of water during perfusion at 10 ml/min, although once again bladder drainage had a significant effect upon the result (Fig. 5).

Discussion

Ureteric dilatation in response to intubation was noted by Wiseman (1934) and has been used therapeutically to increase ureteric diameters for instrumental examination of the lumen (Perez-Castro and Martinez-Pinero, 1982). Finney (1982) noted that urinary flow can occur around a double J stent and confirmed that supraphysiological fluid transmission could be accommodated by these stents in an *in vitro* model even in the presence of a simulated obstruction. Mardis *et al.* (1982) showed, experimentally, that side holes along the stent improved the drainage characteristics and found no significant effect of intravesical pressures on upper tract function by radionuclide studies. They concluded that vesicorenal reflux up the stent, although inevitable, was dissipated by fluid efflux through the side holes low in the ureter; renal function was thereby protected. We agree with the findings of Finney (1982), although we were unable to determine any significant difference in fluid transmission characteristics between polyurethane and medical grade silicone stents (Table). These stents caused raised intrapelvic pressures which were exacerbated by diuresis, which decreased with time and were not as marked if smaller stents were used. The hydroureter evident around these stents both clinically and experimentally may be a protective mechanism initiated to minimise intrapelvic pressure changes consequent upon a relative obstruction due to the stent. Reflux does also seem to occur even when side holes are present.

It cannot be stated that the pressure rises observed are prejudicial to renal function, but a combination of ureteric dilatation, peri-stent urinary flow and vesicorenal reflux in association with these may well interfere with ureteric healing (Fig. 6). The macroscopic changes may be due to work hypertrophy consequent upon inefficient peristalsis

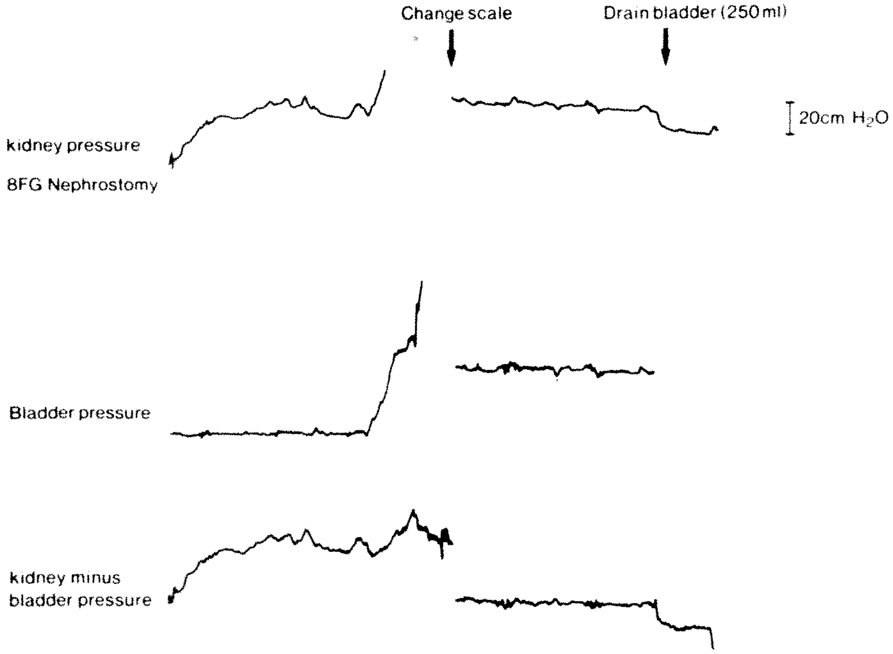
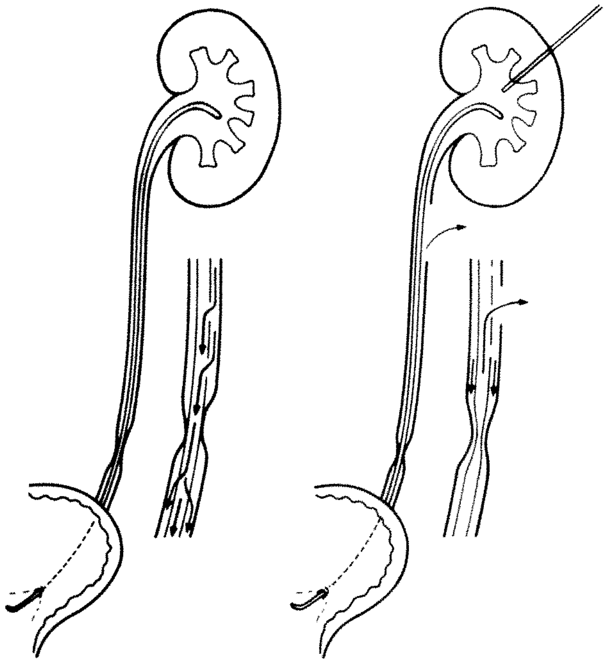


Fig. 5 Tracing from an antegrade pressure flow study (10 ml/min) showing the marked effect of bladder drainage on intrarenal pressure in the presence of a 5 F double J stent.



Distal Obstruction

Distal Obstruction
with fistula

Fig. 6 Effects of double J stents in different clinical situations.

as first described by Drake *et al.* (1962), and the urothelial abnormalities were characteristic of dysplasia associated with the excessive mucus produced by all of the experimentally intubated ureters.

It is concluded that the theoretical flow capabilities of double J stents do not apply when these stents are examined *in vivo*, probably due to urine flow occurring preferentially around rather than through the stent. Reflux also occurs via these catheters. If a double J stent is to be used following ureteric surgery or trauma, we recommend the placement of an ipsilateral nephrostomy drain and a vesical catheter to minimise pressure fluctuations and to limit urinary extravasation in a damaged upper tract.

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The Authors

J. W. A. Ramsay, FRCS, Research Registrar, Department of Urology, St Bartholomew's Hospital.

S. R. Payne, FRCS, Lecturer in Percutaneous Renal Surgery, Institute of Urology

P. T. Gosling, MSc, Senior Physicist, Department of Medical Electronics, St Bartholomew's Hospital.

H. N. Whitfield, MChir, FRCS, Consultant Urologist, St Bartholomew's Hospital.

J. E. A. Wickham, MS, FRCS, Director of Academic Unit, Institute of Urology.

D. A. Levison, MRCPath, Consultant Pathologist, St Bartholomew's Hospital.

Requests for reprints to: J. W. A. Ramsay, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Neurophysiological Measurements in Primary Adult Enuretics

A. FIDAS, N. T. M. GALLOWAY, A. McINNES and G. D. CHISHOLM

University Department of Surgery/Urology and Department of Neurophysiology, Western General Hospital, Edinburgh

Summary—The nerve supply of the lower urinary tract was studied in 25 primary adult enuretics by full urodynamic assessment and neurophysiological measurements. The latter consisted of the measurement of static EMG, sensory thresholds and sacral reflex latencies (SRL). All patients were normal on clinical neurological examination. All neurophysiological measurements were within normal limits in only three patients and the remaining 22 had at least one abnormal response. The commonest abnormality was a high or even absent urethral sensory threshold. These defects in sensory and motor innervation correlated with the clinical dysfunction. It was concluded that this is a valuable method for the detection of nerve defects in the lower urinary tract, especially when the clinical neurological examination is normal.

There is much controversy about the aetiology of nocturnal enuresis. The main debate is whether somatic abnormalities or other factors are more important in the pathophysiology of the disease.

There is increasing evidence that enuretics may have several functional abnormalities which are related to the disorder. Approximately 75% of enuretics have symptoms of frequency, urgency and sometimes urge incontinence due to bladder instability; 25% have normal cystometrograms and no urinary symptoms (Torrens and Collins, 1975; Turner Warwick and Whiteside, 1979).

Another relevant observation is that children with enuresis have a smaller bladder capacity than normal children (Hallman, 1950; Muellner, 1960) but there is no difference in the anatomical bladder capacity (Troup and Hodgson, 1971). This is likely to be due to bladder instability. By studying bladder function during sleep it was found that enuretics have continuous unstable contractions of the bladder which can increase in number and density and lead to enuresis. This does not happen in the normal population (Gastaut and Broughton, 1965; Broughton, 1968).

The relationship between enuresis and the type of sleep is well known, but there is increasing evidence that enuretics do not have sleep patterns different from those of normal controls and that enuretic events are not related to the deep sleep stage but are equally distributed between the different sleep stages, with frequency depending on the time the patient spends in each stage (Kales *et al.*, 1977; Mikkelsen *et al.*, 1980).

These functional disorders, together with the known association between enuresis and hereditary factors, support the view that there is an underlying somatic defect in the aetiology of enuresis, but the nature of the defect is poorly understood.

We have studied the nerve supply of the lower urinary tract in order to detect abnormalities that could be correlated with the clinical features of enuresis in an attempt to determine the pathophysiology. We measured the sensory thresholds and sacral reflex latencies. This is a sensitive method capable of detecting nerve abnormalities where the standard neurological examination fails.

Patients and Methods

Twenty-five adult enuretics were studied. All pre-

Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

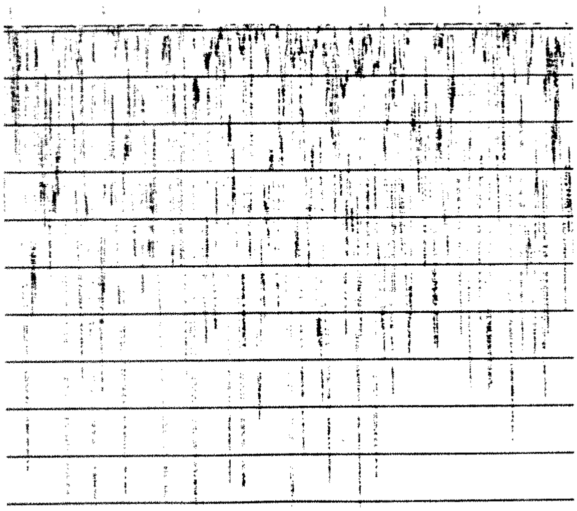

Fig. 1 Static EMG during gripping. Upper trace anal sphincter. Lower trace urethral sphincter. Full interference pattern—normal.

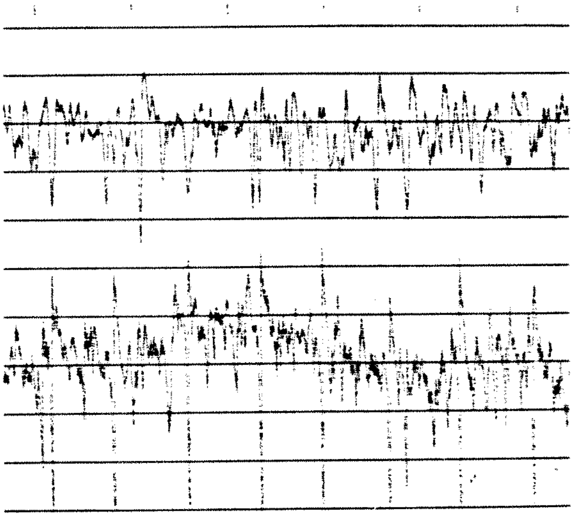

Fig. 2 Electromyography. Upper trace anal. Lower trace urethral sphincters showing poor interference pattern with large (150 uv) units suggesting reinnervation.

sented with enuresis occurring at least once a month and all were normal on routine clinical neurological examination. There were 13 males and 12 females. Their ages ranged from 15 to 53 years (median 28.2).

The method has been described in detail by Galloway *et al.* (1985) and is now briefly described.

A DISA 1500 EMG averager system, a ring catheter mounted electrode, an anal plug with ring electrodes and a stimulator were used.

The procedure consisted of

(i) Static EMG study of the urethra and anal sphincters with the patient (a) relaxed, (b) gripping and (c) coughing (Figs 1 and 2).

(ii) Measurement of sensory thresholds of the dorsal nerve of the penis/clitoris and urethra. This was done by applying an electrical stimulus of 0.1 ms duration in a frequency of 2 stimuli/s, increased from 0 mA until felt by the patient. It was repeated at least 3 times to obtain a standard value that could then be accepted as the sensory threshold.

(iii) Electrical measurement of sacral reflexes using a stimulus = sensory threshold × 3 (Figs 3 and 4):
(a) From the dorsal nerve of the penis/clitoris to the urethra.
(b) From the dorsal nerve of the penis/clitoris to the anal sphincter.
(c) From the urethra to the anal sphincter.

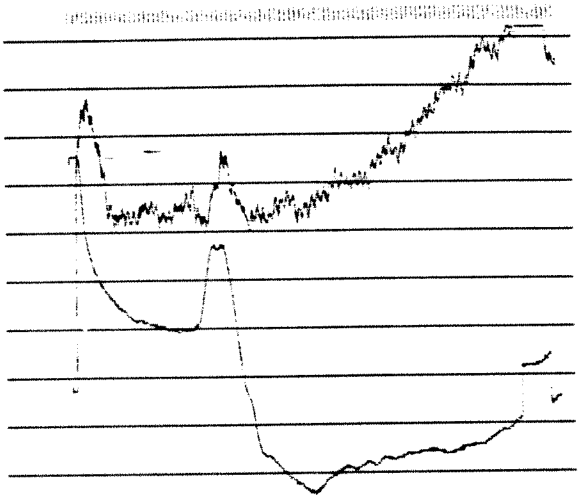

Fig. 3 Dorsal nerve stimulation and activity recorded at both anal and urethral sphincter—average 100 times. Upper trace anus, lower trace urethra. Normal responses. Peak at 32 ms for both.

These were repeated until exactly the same response was obtained. If this was not the case, or if the response was absent, the intensity of the stimulus was increased until it became uncomfortable for the patient or until 99 mA. If no stable response was produced the response was considered absent.

Results

Six patients had stable bladders, 15 were unstable

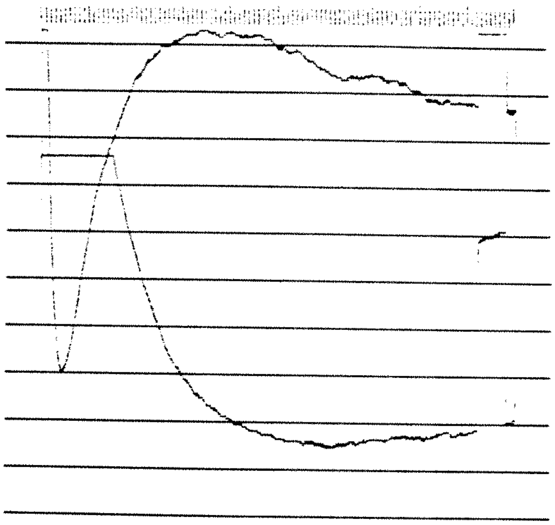

Fig. 4 Dorsal nerve stimulation and activity recorded at both anal and urethral sphincter—average 100 times. Upper trace anus, lower trace urethra. Absent response.

and 4 were not studied with videocystometry, but all had daily symptoms suggesting they were unstable.

The EMG was characterised as normal, fair and poor. Fair (Fig. 1) and poor were both abnormal. The degree of abnormality was based on a visual assessment of the interference pattern. As in most muscles, no baseline is seen during maximum contractions. **Fair** was where a significant amount of baseline was seen and **poor** was where most of the trace was baseline.

We studied 59 volunteers with no urinary symptoms in order to establish the normal limits. They comprised doctors and also patients awaiting vasectomy, with renal or gallbladder stones, small inguinal hernias and proven psychological impotence. Twenty-one had a full study and 38 had only the anal latency after dorsal nerve stimulation. The means with standard deviations are shown in Tables 1 and 2. Our working normal values are presented in Table 3. They are at least two standard deviations different from the mean of the controls.

Table 1 Control Patients (n = 21)

Dorsal nerve stimulation	
Sensory threshold (mV)	6.1 + 0.6
Anal latency (ms)	40.2 + 2.7
Urethral latency (ms)	39.8 + 2.9
Urethral stimulation	
Sensory threshold (mV)	8.1 + 1.2
Latency to anus (ms)	68.9 + 4.1

Table 2 Control Patients (n = 38)

Dorsal nerve stimulation	
Anal latency	38.5 + 5.8 ms

Table 3 Neurophysiological Measurements: Working Normal Values

Dorsal nerve stimulation	
Sensory threshold	≤ 10 mV
Anal latency	≤ 50 ms
Urethral latency	≤ 50 ms
Urethral stimulation	
Sensory threshold	≤ 10 mV
Latency to anus	≤ 80 ms

Tables 4 and 5 present detailed results in 25 enuretics with the static EMG, sensory thresholds, latencies and cystometry.

Tables 6, 7 and 8 summarise the results according to the reflex arc which was studied.

If we consider as normal those patients in whom all neurophysiological measurements were within normal limits, then only three were normal. These patients also were stable in cystometry and had no other urinary tract symptoms. The remaining 22 patients had at least one abnormal response. The main abnormality was the urethral sensory threshold, which was normal in only four patients, and absent in four of those with abnormal responses.

Finally, four patients had a slightly abnormal urethral threshold with normal latencies, normal dorsal nerve threshold and normal EMG, but were unstable on videocystometry.

Discussion

The sacral reflexes are present in all people. Their presence or absence reflects the integrity of sacral reflex pathways. This can be absent when nerves are cut or severely damaged and sometimes after relatively minor damage. This latter is presumably due to a temporal dispersion of the barrage of impulses causing failure of the reflex. The reflex may also be absent in developmental lesions, *e.g.* myelodysplasia. The response is usually delayed in less severe nerve lesions. No inference can be made about the source of damage, though one would expect delay in a diabetic due to demyelination. The response can be delayed in developmental lesions when the stimulus has to pass through more interneurons or make an abnormally long arc.

Table 4 Neurophysiological Measurements in 25 Primary Adult Enuretics

Stimulation of dorsal nerve of penis/clitoris				*Stimulation of urethra*	
EMG	*Sensory threshold (mA)*	*Urethral latency (ms)*	*Anal latency (ms)*	*Sensory threshold (mA)*	*Latency (ms)*
N Stable	8	33	33	10	70
N Stable	9.4	42	39	9	54
P Stable	6.5	ABS	ABS	ABS	ABS
N Unstable	4.7	60	60	ABS	60
N Unstable	5.5	40	35	13	70
N Unstable	7.3	38	38	ABS	75
N Unstable	5.8	40	43	31	—
F ?	70	64	62	28	70
P ?	9.5	45	40	6.5	ABS
P Stable	3	60	40	—	70
N ?	14	70	50	21	112
N Unstable	5.5	40	40	17	68
P Unstable	5.5	ABS	ABS	ABS	ABS
N Unstable	6	62	40	15	80
P Unstable	4.5	50	60	30	ABS
N Stable	5.6	70	60	13	65
N Unstable	ABS	51	50	8	80
N Stable	6	42	—	—	—
N ?	6.6	ABS	—	—	—
N Unstable	6.5	38	35	13	50
F Unstable	20	—	58	—	—
— Unstable	15	50	55	15	65
F Unstable	8	42	50	12	95
— Unstable	10	42	45	22	65
—	28	65	45	25	74

N = Normal. F = Fair. P = Poor. ABS = Absent.

Table 5 Results in 25 Enuretics

Normal	3
Abnormal	22
Total	25

Table 6 Static EMG Results in 25 Enuretics

Normal	*Abnormal*	*Not recorded*
14	3 Fair 8 5 Poor	3

Table 7 Sensory Thresholds in 25 Enuretics

		Normal	*Raised*	*Absent*	*Not recorded*
Sensory thresholds	Dorsal nerve	19	5	1	—
	Urethra	4	13	4	4

Table 8 Latencies in 25 Enuretics

Latency	*Normal*	*Delayed*	*Absent*	*Not recorded*
Dorsal nerve to urethra	13	8	3	1
Dorsal nerve to anus	15	6	2	2
Urethra to anus	15	2	4	4

High thresholds imply a disturbance of sensory nerves which may of course be more proximal than S2 lesions.

Our results suggest that many enuretics have a sacral neurological deficit which can be both sensory and motor. The major deficit is usually sensory and this is readily documented using neurophysiological techniques. Our findings agree with those of McGuire and Savastano (1984), who showed that 50 of 55 enuretics had poor cerebral appreciation of the degree of bladder filling during filling cystometry and were unaware of detrusor contractility and the prodromal reflex events of the detrusor contraction which involved a decrease in EMG activity and urethral closure pressure. We observed the same abnormalities in nearly all of our patients. The phenomenon of diminished appreciation of the bladder events with an overactive bladder has been called hypo-aesthetic urgency (Yeates, 1972).

The severity of the neurological deficit is not constant. Some patients have a profound sensory loss. Four patients were unaware of stimulation to the urethra and others had thresholds near or within normal limits. The same was found for the latencies. This variation in neurological deficit may explain the variable severity of enuresis because this neurological deficit may provide the organic basis of nocturnal enuresis. Our results cannot exclude nerve defects at higher levels in enuretics with normal responses because our method can be applied only distal to the S1 levels. Sensory defects can be at higher levels than S1, especially when there are normal SRL with abnormal sensory thresholds.

It is concluded that the function of sacral nerve segments of the cord is deficient in most enuretics. These abnormalities suggest that sacral cord structures may be deficient in these patients. Some may never acquire normal control of micturition because the structures are absent. Others may be slow to develop either the full ability to control their lower urinary tract or an acceptable pattern of behaviour. Another group may have the necessary structures but because of adverse factors or inappropriate training there is a delay before they have normal control of micturition.

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The Authors

A. Fidas, MD, Honorary Urological Registrar.

N. T. M. Galloway, FRCS, formerly Lecturer in Urology. Now Senior Registrar, Department of Urology, Royal Infirmary, Cardiff.

A. McInnes, MRCP, Consultant in Clinical Neurophysiology.

G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery and Honorary Consultant Urologist.

Requests for reprints to: G. D. Chisholm, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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"Clam" Ileocystoplasty for the Treatment of Refractory Urge Incontinence

A. R. MUNDY and T. P. STEPHENSON

Departments of Surgery and Urology, Guy's Hospital, London; Department of Urology, Royal Infirmary, Cardiff

Summary—Forty patients with refractory urge incontinence were treated by "clam" ileocystoplasty. Thirty patients were cured of their symptoms and are voiding spontaneously, six were cured of their symptoms and are on clean intermittent self-catheterisation and four had their symptoms significantly improved by the operation.

Bladder compliance is usually improved by the operation and detrusor instability is either abolished or reduced to an insignificant level, but voiding dysfunction is a common post-operative problem and must be identified and treated.

Urge incontinence is a common clinical problem. Most patients respond to either bladder drill (Holmes *et al.*, 1983) or to pharmacological treatment with anticholinergic drugs, particularly oxybutynin (Mundy, 1985a), at least in the short term. When these methods fail, transvesical injection of the pelvic plexuses with phenol is a useful technique in women (Blackford *et al.*, 1984) but there is a significant failure rate in the age group in which the problem is most commonly found and in any case the technique is not applicable to men because of the risk of impotence.

There is a need for a treatment that can be used when the phenol technique is either ineffective or contraindicated. Bramble (1982) reported good results with augmentation cystoplasty in this type of patient. For the last 3 years we have been using the technique and have more recently expanded the indications for the procedure to include patients who would otherwise have been treated by substitution cystoplasty (Stephenson and Mundy, 1985) or some other more major surgical procedure.

We report our experience with the "clam" technique in 40 consecutive patients with refractory urge incontinence.

Patients and Methods

There were 40 patients, 18 male and 22 female, with an age range of 6 to 57 years (mean age 28). Of these 40, 35 presented with urge or urge incontinence and five were totally wet. Eight patients had an overt neuropathy, 25 had no evidence of a neuropathy, five were suspected of having a neuropathy from urodynamic data, one had an imperforate anus and one had suffered severe pelvic trauma.

Pre-operative videourodynamic studies in 18 patients showed detrusor instability or hyperreflexia, eight had poor bladder compliance and 14 had both instability and poor compliance.

Previous treatment for these patients is shown in Table 1.

The technique has been described elsewhere (Bramble, 1982; Mundy, 1985b), but several points deserve to be emphasised. The bladder is opened like a clam in the coronal plane along its maximal

Table 1 Previous Treatment

Oxybutynin	28
Other drugs	9
"Phenol"	12
Bladder transection	5
Urinary diversion	4
Artificial sphincter	3
Colposuspension	3

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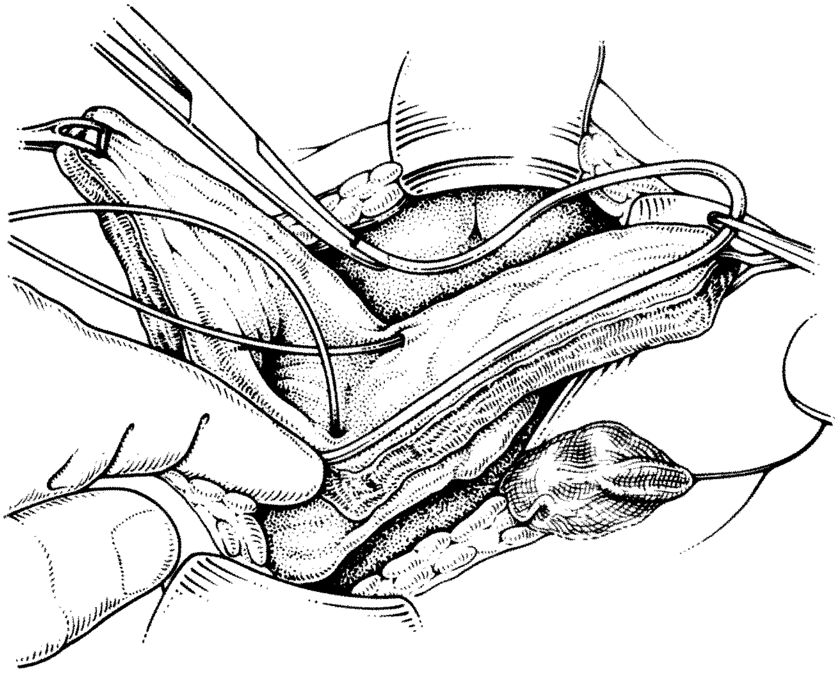

Fig. 1 Clam cystoplasty technique 1—the bladder is opened in the coronal plane; the ureteric orifices have both been catheterised. The maximal bladder circumference is being measured with a length of vinyl tubing to determine the length of the ileal segment to be isolated to form the cystoplasty patch.

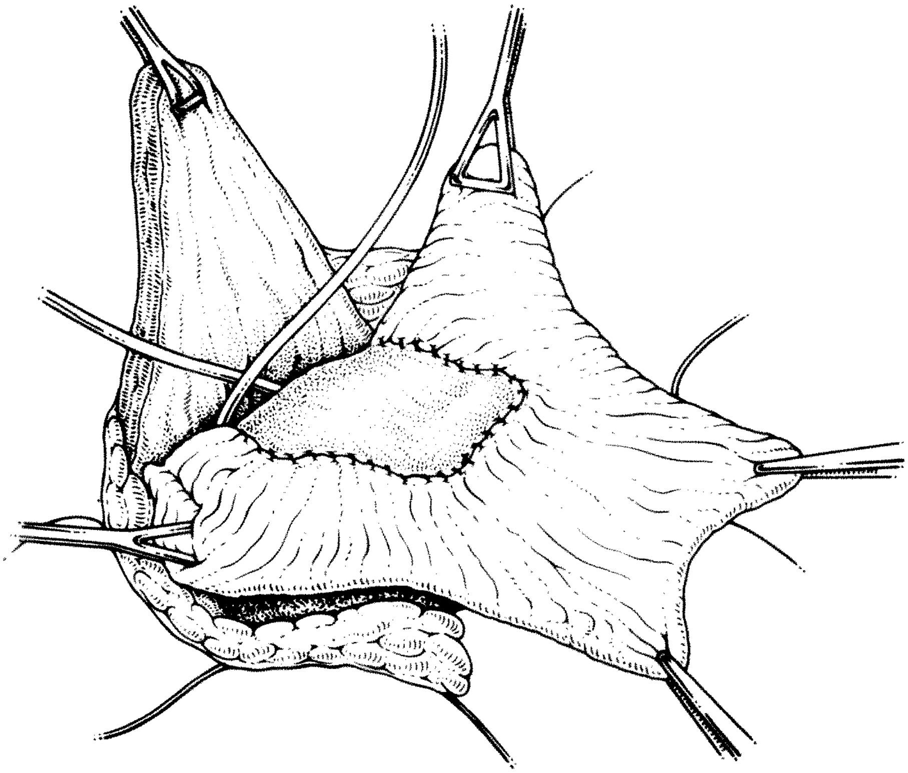

Fig. 2 Clam cystoplasty technique 2—the ileal patch has been sutured to the posterior half of the bladder.

circumference, which is along the line of attachment of the fascial wing that attaches the bladder to the iliac vessels, from a point 1 to 2 cm in front of one ureteric orifice and about 2 cm from the bladder neck to a similar point on the other side (Fig. 1). A section of terminal ileum equal in length to the measured maximal circumference of the opened bladder is then isolated on its vascular pedicle, opened along its antimesenteric border to form a patch, triangulated at each end and sewn in place with one layer of continuous absorbable suture material (Fig. 2). A suprapubic catheter is left in the bladder at the end of the procedure, clamped after 8 days to allow spontaneous voiding and removed when adequate emptying without undue frequency is established.

All patients had a repeat videourodynamic evaluation at 3 months and any voiding dysfunction was treated on the basis of that investigation.

Thirteen patients had a second procedure at the time of their clam cystoplasty (Table 2).

Table 2 Associated Procedures

Implantation of artificial sphincter (AUS)	5
Undiversion	4
Bladder neck incision	2
Colposuspension	1
Change of AUS pressure balloon	1

Results

Thirty-six patients (90%) have been cured of their symptoms; 30 of these are voiding spontaneously, six by clean intermittent self-catheterisation (CISC). The four remaining patients all have a degree of stress incontinence: one of them is now dry following implantation of an artificial sphincter and another has a degree of urge incontinence. Follow-up is from 3 to 39 months with a mean of 12 months.

Voiding dysfunction was the commonest problem (Table 3) and occurred in 13 patients, including the six using CISC. Voiding dysfunction was relieved in the other seven patients by a selective sphincterotomy in five, a selective sphincterotomy with bladder neck incision in one and a bladder neck incision alone in one. Mucus retention was a significant problem in only one (male) patient who required a cystoscopy to wash out an unusually large plug of inspissated mucus 4 months after operation. Surgical problems related to the procedure occurred in only two patients; one had a persistent urine leak requiring surgical closure and the other developed small bowel obstruction requiring a laparotomy 7 months post-operatively.

Table 3 Complications

Voiding dysfunction	7 (13)*
Stress incontinence	3
Recurrent UTI	2
AUS problems	1
Mucus plug retention	1
Small bowel obstruction	1
Persistent urine leak	1

* Including the 6 patients using CISC.

Thirty-one patients have had follow-up VUD studies, seven await their studies and two have not been restudied, one for technical reasons and the other because of currently severe ischaemic heart disease of recent onset (Table 4). Bladder compliance was low pre-operatively in 20 patients restudied, in 14 (70%) of whom it was normal when restudied. Five patients were improved but were still poorly compliant and one patient had worse compliance than beforehand. Two patients with previously normal compliance became poorly compliant.

Table 4 Postoperative Videourodynamic Findings in 31 Patients

Compliance	Normal, previousl abnormal	14
	Normal, previously normal	9
	Persistently poor but improved	5
	Worse (2 previously normal)	3
Instability	Abolished	15
	Absent, previously absent	5
	Persistent but no longer significant	11
Capacity	400-1000 ml, mean 615 ml	
Residual	50-400 ml, mean 175 ml	14
	Absent, voiding spontaneously	11
	Absent, CISC	6
Voiding pressure	20-80 cm H_2O, mean 39 cm H_2O	15
	Voiding by straining	10
	CISC	6
Peak flow rate	10-45 ml/s, mean 22 ml/s	15*
	10-30 ml/s, mean 17 ml/s	10**

* Refers to the 15 who have a voiding detrusor contraction.
** Refers to the 10 who void entirely by straining.

Of the 26 previously unstable or hyper-reflexic patients, 15 had the instability or hyper-reflexia abolished and 11 had persistent instability, although in all cases the instability was asympto-

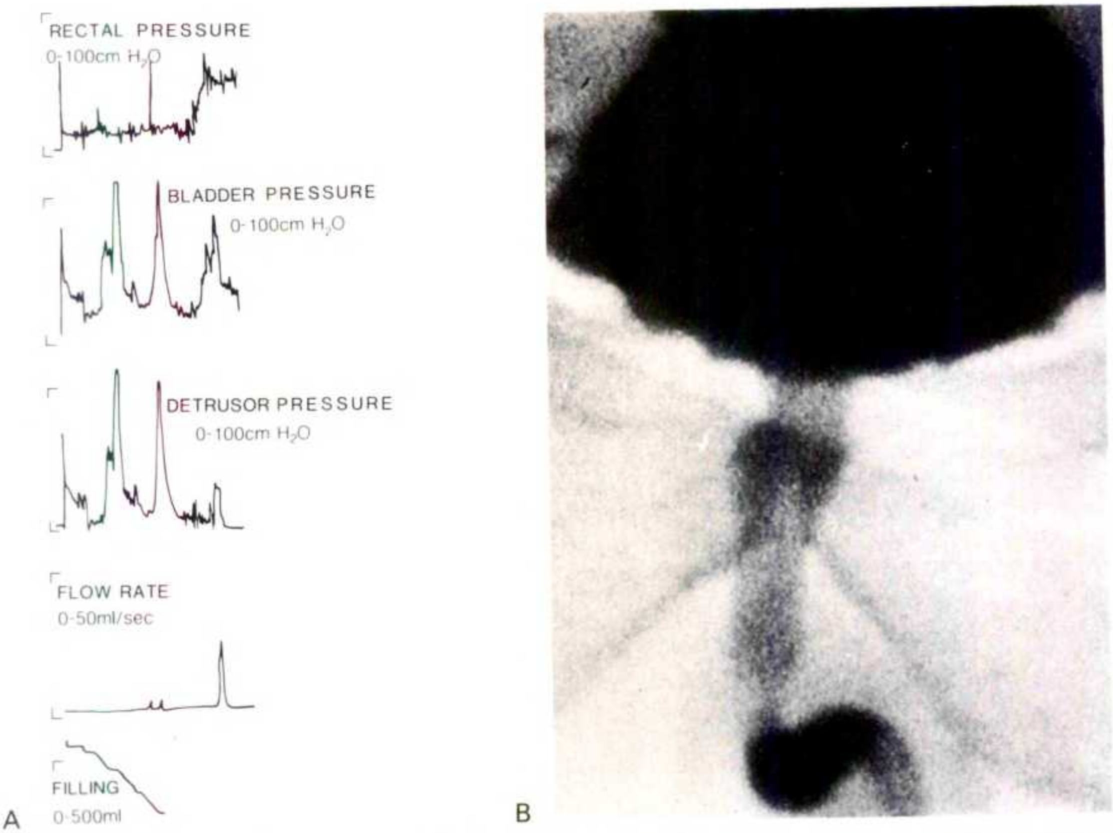

Fig. 3 (A) The pre-operative urodynamic trace and (B) the video appearance of the bladder of a 42-year-old man with detrusor instability.

matic and below the 15 cm H_2O level generally (but arguably) regarded as the level at which it becomes urodynamically significant (Figs 3 and 4).

Mean bladder capacity was increased from 280 to 615 ml. Twenty of the 31 patients (65%) had residual urine post-operatively with a mean volume of 175 ml which represented approximately 25% of the total bladder capacity. Mean *functional* bladder capacity was therefore increased from 280 to 440 ml.

Discussion

These results confirm the value of the "clam" cystoplasty as treatment of refractory urge incontinence. All patients were improved, if not cured of their symptoms, albeit with the proviso that voiding dysfunction is a common post-operative problem that requires careful follow-up.

Presumably, since unstable activity is frequently found at a much reduced amplitude post-operatively and since voiding dysfunction is so common, the procedure works by interposing a section of tissue that absorbs detrusor contractile activity, thereby making unstable activity ineffective and voluntary voiding activity inefficient. That being the case, all that is required is to provide a segment of supple and viable tissue that will remain as such but will contribute nothing in itself to post-operative bladder function. Although cases of malignancy have been reported with ileocystoplasty segments (Stone *et al.*, 1985), the malignant potential of ileal segments in contact with urine would appear to be less than that of sigmoid segments in contact with urine (Leadbetter *et al.*, 1979), although this may apply only to ureterosigmoidostomies where the urinary and faecal streams are mixed. Nonetheless, colonic surgery is generally accepted as carrying a higher complication rate than ileal surgery and for this reason we prefer to use an ileal segment to form the cystoplasty patch.

Given the presumed way in which the "clam" cystoplasty produces its beneficial effect, by making detrusor activity relatively inefficient, it is not surprising that voiding dysfunction is so common

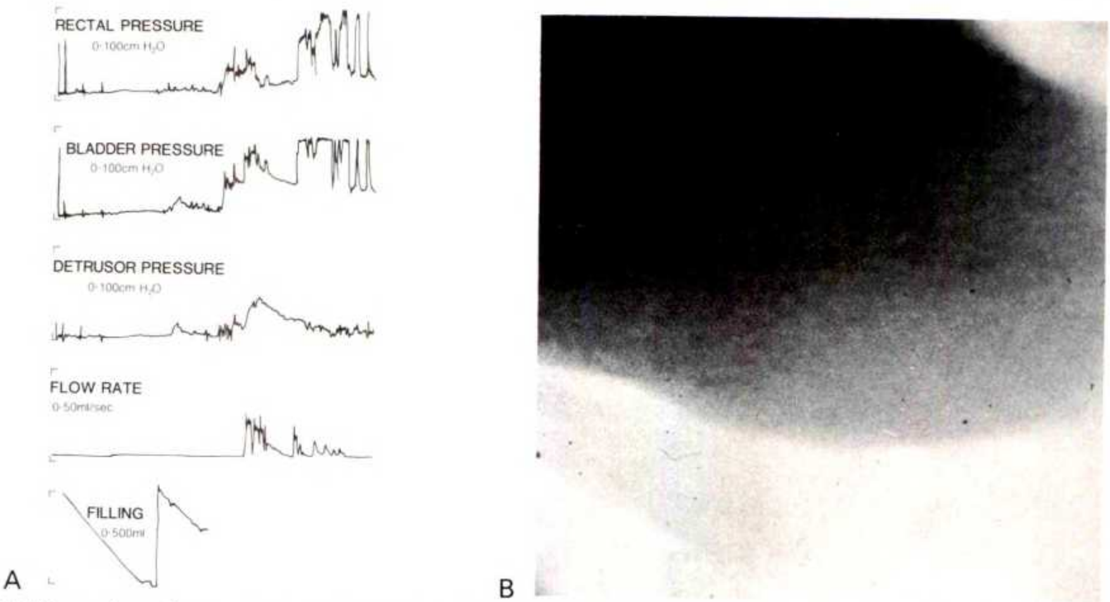

Fig. 4 (A) The urodynamic trace and (B) the video appearance of the bladder of the same man as in Figure 3, 6 months after a "clam" ileocystoplasty.

post-operatively. Only one male patient (from early in the series) still has a competent bladder neck; all of the rest either had bladder neck incompetence or a previous bladder neck incision seen on their pre-operative urodynamic study or required a bladder neck incision (at least) post-operatively. It is now our practice to perform bladder neck incision routinely in males, either at the time of operation or beforehand. The finding that seven of the 34 patients (21%) who void spontaneously required sphincter balancing procedures post-operatively emphasises the need for careful urodynamic follow-up in the early post-operative period. This percentage rises to 35% (7/20) if the 14 patients who subsequently voided spontaneously who had signs of sphincter weakness on their pre-operative VUD studies are taken into acount as a group who would not be expected to need to have a procedure to reduce their outflow resistance.

The latter observation, coupled with the finding that only three of the 14 had problems with stress incontinence after their "clam", suggests that sphincter weakness of a mild degree should not be treated at the time of the "clam" as it is unlikely to be a persistent problem. Indeed it may be regarded as an asset since it makes the patient less prone to develop a post-operative voiding dysfunction.

It is also worth noting that most patients require a stabilisation period of 3 months after a "clam" to allow the balance between bladder and urethral behaviour to become established. During this period many instances of voiding dysfunction will resolve spontaneously as post-operative discomfort settles and as the patients learn how to use their augmented bladders efficiently. In patients with more severe voiding difficulties, CISC is useful as a temporary measure during this period until spontaneous voiding is established.

Such has been our experience with the clam technique that we have begun to use it in patients who would previously have been treated by substitution cystoplasty. Thus, in a patient with a neuropathic bladder who has normal upper tracts and a relatively normal bladder capacity and bladder wall thickness, we would now use the clam technique in preference to substitution cystoplasty. This particularly applies to patients, with or without neuropathy, who have poor compliance as their predominant urodynamic abnormality. These patients often suffer severe symptoms and are usually unresponsive to any lesser form of treatment. They are particularly worrying because the sustained elevated intravesical pressures or the intrinsic bladder abnormality itself or both often progress to cause impaired upper urinary tract function (Stephenson and Mundy, 1985). Nonetheless, we have always felt that it should be possible to treat them by something less than subtotal cystectomy and substitution cystoplasty. The "clam" procedure would appear to be the answer.

For patients with urge incontinence due to detrusor instability and those with similar symptoms and urodynamic abnormalities associated with an overt neuropathy, we now feel able to offer a rational scheme of management. The first line of treatment would be bladder drill if a patient has sufficient sphincter control to be able to resist the unstable contractions. If not we would supplement bladder drill with oxybutynin 5 to 10 mg three or four times a day. For women who fail to respond to this we would suggest transvesical injection of the pelvic plexuses with phenol. For those women in whom the phenol technique fails and for men in whom the phenol technique is contraindicated, because of the risk of impotence, we would recommend "clam" ileocystoplasty. In this way we feel able to help most if not all of our patients with this distressing symptom.

Acknowledgement

Figures 1 and 2 were drawn by Philip Wilson.

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The Authors

A. R. Mundy, MS, FRCS, MRCP, Senior Lecturer in Urology and Consultant Urological Surgeon, Guy's Hospital.

T. P. Stephenson, MS, FRCS, Consultant Urological Surgeon, Cardiff Royal Infirmary.

Requests for reprints to: A. R. Mundy, Department of Urology, Guy's Hospital, London SE1 9RT.

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Sphincter Behaviour in Myelomeningocele

A. R. MUNDY, P. J. R. SHAH, M. BORZYSKOWSKI and H. M. SAXTON

Departments of Surgery, Urology, Paediatrics and Radiology, Guy's Hospital, London

Summary—Four hundred and two videourodynamic studies were performed on 207 children with neuropathic vesicourethral dysfunction due to myelomeningocele. The children were divided into three groups (contractile, intermediate and acontractile) according to the urodynamic behaviour of their bladders, and the behaviour of the bladder neck and distal sphincter mechanism was assessed in each group.

The bladder neck may be competent or incompetent in children with contractile bladders but is never obstructive, and is always incompetent in children with either intermediate or acontractile bladders at their usual bladder volumes. The distal sphincter mechanism is nearly always dynamically obstructive (detrusor-sphincter dyssynergia) in children with contractile bladders but is rarely if ever incompetent, whereas in children with intermediate or acontractile bladders, both (static) distal sphincter obstruction and sphincter weakness incontinence exist to some degree, although the predominance of one of these may mask the existence of the other unless it is specifically looked for or some therapeutic manoeuvre unmasks it.

The main conclusion from this study is that, with the possible exception of those few children with more minor partial cord lesions, dysfunction of one or both sphincter mechanisms is the rule in congenital cord lesions.

The term "neuropathic bladder" implies that the major, if not the only urodynamic abnormality in such a situation is in the bladder, with the urethra contributing little if anything to the clinical picture. It has become apparent that this is not the case. The phenomenon of detrusor-sphincter dyssynergia is now widely recognised as a common cause of outflow obstruction in neuropathy (Mundy *et al.*, 1982; Rickwood, 1984; Thomas, 1984) and, at the other extreme, interest in the artificial sphincter has highlighted the incidence of sphincter weakness incontinence. On the other hand, although the available evidence suggests that urethral dysfunction is a common occurrence in neuropathy, there are no published studies of the incidence and significance of the various urethral functional abnormalities that may occur and their relationship to the neuropathic bladder dysfunction.

Our experience of surgical reconstruction of the lower urinary tract in neuropathy (Mundy and Stephenson, 1984; Stephenson and Mundy, 1985) has led us to look carefully at urethral dysfunction in these patients. This report describes our findings on the incidence of urethral dysfunction, the types of dysfunction that occur and their interrelationship with each other and with the other urodynamic abnormalities.

Patients and Methods

In the last 5 years we have performed videourodynamic studies (VUD) in 207 children aged 1 month to 16 years with congenital cord lesions and associated vesicourethral dysfunction. In each case detrusor behaviour was classified as contractile (Fig. 1), intermediate (Fig. 2) or acontractile (Fig. 3) according to whether or not the detrusor was able to contract and whether, if present, such contraction was capable of giving any useful degree of bladder emptying (Table 1).

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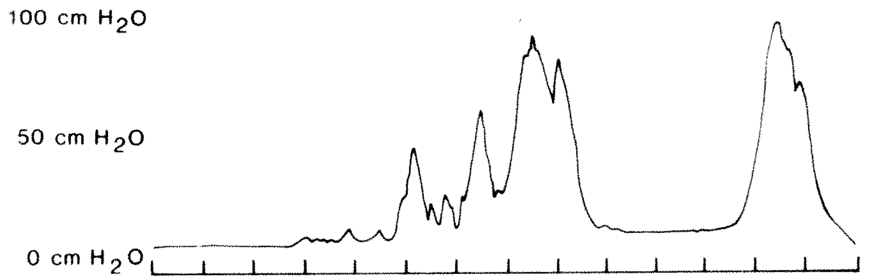

Fig. 1 Subtracted detrusor pressure trace of patient with contractile bladder showing waves of detrusor pressure of sufficient amplitude and duration to be capable of giving a useful degree of bladder emptying.

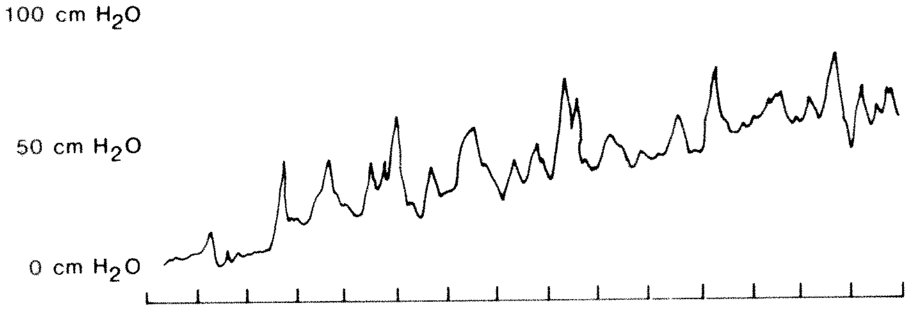

Fig. 2 Subtracted detrusor pressure trace of patient with intermediate bladder showing detrusor contractile activity but not of sufficient amplitude or duration to be capable of giving a useful degree of bladder emptying.

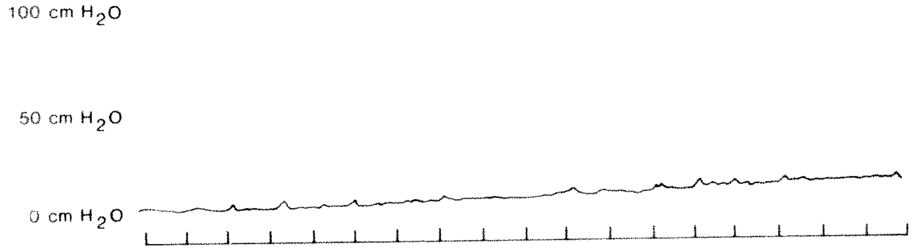

Fig. 3 Subtracted detrusor pressure trace of patient with acontractile bladder showing the absence of detrusor contractile activity.

Table 1 Incidence of the Various Types of Bladder Dysfunction

Contractile—	detrusor activity capable of giving useful bladder emptying	73 children
Intermediate—	detrusor activity present but insufficient to cause useful bladder emptying	82 children
Acontractile—	no demonstrable detrusor activity	52 children

Bladder neck and distal sphincter behaviour was determined in each patient primarily on the basis of video assessment. The bladder neck was classified as competent or incompetent, depending on its appearance and cough/strain competence at a time when the detrusor was not contracting. Distal sphincter behaviour was assessed similarly during the filling phase; during voiding the degree of opening of the sphincter-active urethra was assessed. In some patients these studies were supplemented by concentric needle EMG studies (28 patients) or by dynamic urethral pressure profiles (32 patients) of the distal sphincter mechanism (Stephenson, 1984).

Of the 207 children, 143 have been restudied one or more times by VUD, including all of the children who have had surgical intervention or who are using clean intermittent self-catheterisation (CISC). As a result there were 402 studies available for review.

Results

Contractile bladders (Table 2)

Seventy-three children (35%) were in this category. The bladder neck was competent in 38 (52%) and incompetent in 35 (48%). Detrusor sphincter dys-

Table 2 Sphincter Dysfunction in the Contractile Group (73 children)

Bladder neck	Competent	38 (52%)
	Incompetent	35 (48%)
	Obstructive	0
Distal sphincter mechanism	Competent	73 (100%)
	Incompetent	0
	Obstructive	69 (95%)
	Voluntary control	16 (22%)

synergia (DSD) was present in 69 (95%) as judged, on the video study, by a failure of relaxation of the sphincter-active urethra during a detrusor contraction, a progressive bulging of the urethra above the non-relaxing zone during the upstroke of the detrusor contraction and a tendency for the maximum flow to occur during the downstroke of the detrusor contraction (Fig. 4). When the video studies were correlated with the information derived from the EMG and dynamic urethral pressure studies, it was found that urethral activity during a detrusor contraction usually (48 patients) took the form shown in Figure 5a, with a rise in urethral pressure and sphincter EMG activity concurrent with the rise in detrusor pressure but with a rapid, albeit incomplete, fall-off allowing voiding during the declining-pressure phase of the detrusor contraction. In 21 patients a more clonic pattern of urethral activity was seen (Fig. 5b) associated with the video appearance of fluttering of the sphincter-active urethra.

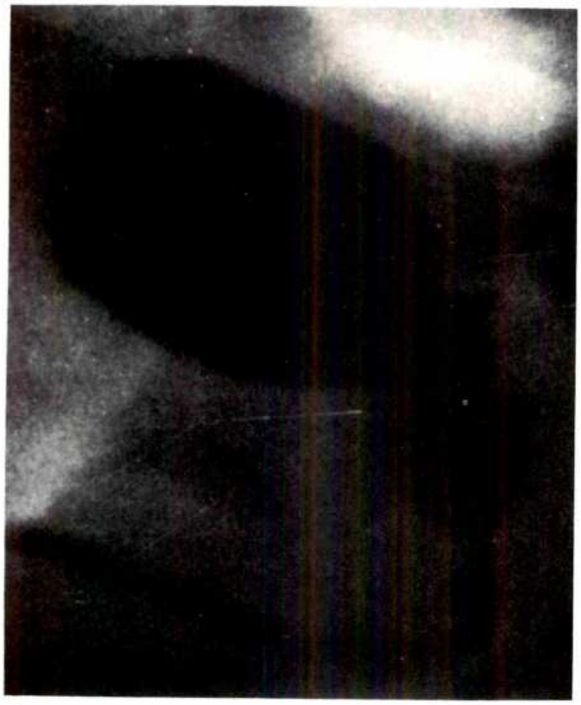

Fig. 4 VUD appearances of bladder outflow in patient with contractile bladder and detrusor-sphincter dyssynergia.

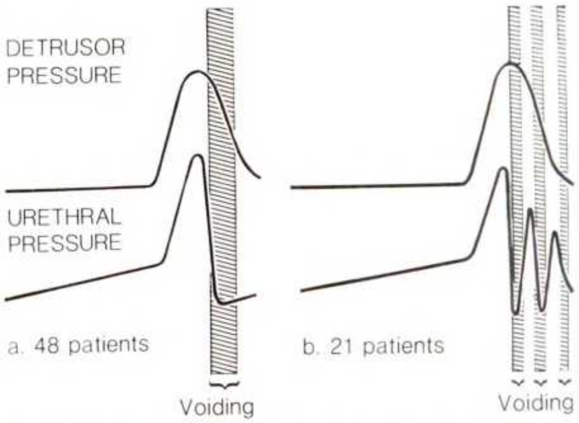

Fig. 5 The two patterns of urethral behaviour observed during detrusor contractions in patients with contractile bladders and detrusor-sphincter dyssynergia.

Voluntary, though limited, control of distal sphincter activity, presumably by virtue of pelvic floor control, was present in 16 children (22%). These were children with partial cord lesions, most of whom had normal anal tone, positive sacral reflexes and, when assessable, voluntary anal sphincter activity, and included all of the children with no apparent DSD.

Intermediate bladders (Table 3)

There were 82 children (40%) in this group. The bladder neck was incompetent in all of them unless the bladder was emptied to a volume below their usual residual urine volume, in which case apparent bladder neck competence was often seen. Subsequent total sphincteric incompetence was related to a rise in bladder pressure which, on the video studies, caused a progressive funnelling of the sphincter-active urethra until leakage occurred (Fig. 6). This is in contrast to the much more dyna-

Table 3 Sphincter Dysfunction in the Intermediate Group (82 children)

Bladder neck	Competent	0
	Incompetent	82 (100%)
	Obstructive	0
Distal sphincter mechanism	Competent	0
	Incompetent	82 (100%)
	Obstructive	82 (100%)
	Voluntary control	0

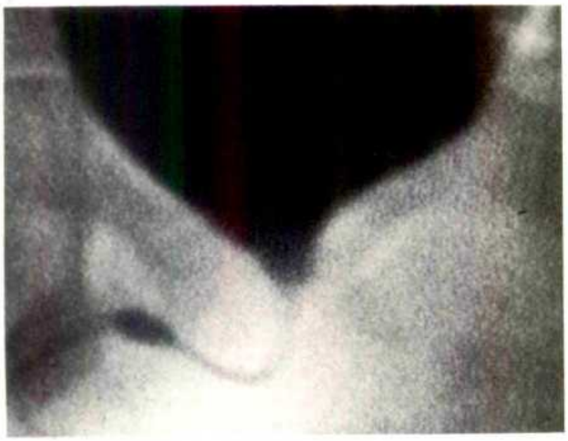

Fig. 6 VUD appearances of bladder outflow in patient with intermediate bladder and static distal sphincter obstruction (contrast with Fig. 4).

mic changes seen in the activity of the sphincter-active urethra in the contractile group with DSD. There was no active opening of the distal sphincter mechanism when urine leakage occurred and, as far as could be seen on EMG and dynamic urethral pressure studies, very little change in sphincter activity at all, throughout filling and emptying, apart from a degree of fluctuation around the base-line urethral pressure which mirrored the detrusor pressure fluctuations. There was no useful degree of voluntary control of the distal sphincter mechanism.

Acontractile bladders (Table 4)

There were 52 children (25%) in this group. As in the intermediate group, the bladder neck was incompetent in all children at their usual bladder volumes, but as distinct from the intermediate group the onset of total sphincteric incompetence was more dependent on bladder volume than pressure. As in the intermediate group, distal sphincter behaviour appeared static, indeed even more so, with no apparent difference in urethral pressure between filling and attempted voiding. As in the intermediate group, there was no useful degree of voluntary control of the distal sphincter mechanism.

Table 4 Sphincter Behaviour in the Acontractile Group (52 children)

Bladder neck	Competent	0
	Incompetent	52 (100%)
	Obstructive	0
Distal sphincter mechanism	Competent	0
	Incompetent	52 (100%)
	Obstructive	39 (75%)
	Voluntary control	0

In no patient, in any group, was true, dyssynergic bladder neck obstruction seen.

Discussion

In children with contractile bladders the dysfunction of the distal sphincter mechanism is a dynamic obstruction—detrusor-sphincter dyssynergia. With acontractile and intermediate bladders, distal sphincter activity by contrast seems to be more static and relatively unchanging, exhibiting both obstruction and sphincter incompetence, depending on whether intravesical pressure is below or above (respectively) the pressure exerted by the sphincter-active urethra. Because of this more static nature we call this a "static distal sphincter obstruction". Depending on the exact pressure exerted by the distal sphincter and the detrusor and extravesical pressures to which it is subjected, either the obstruction or the sphincter incompetence may predominate, but both will almost always be present and the relative importance of each may change (see below). In general it might be said that the quality of sphincter activity correlates fairly well with the quality of detrusor activity such that in intermediate bladders greater detrusor contractility correlates with greater urethral activity, so that static distal sphincter obstruction predominates but sphincter weakness is nevertheless present to allow what bladder emptying there is to occur. Equally in acontractile bladders, lack of detrusor activity is mirrored by lack of urethral activity and so sphincter weakness predominates, but the presence of static distal sphincter obstruction is shown by the presence of residual urine.

In intermediate and acontractile bladder dysfunction the bladder neck is always incompetent at usual bladder volumes and in contractile dysfunction it is also incompetent in almost half of the patients. Bladder neck obstruction, by contrast, is never seen.

We have found that an incompetent bladder neck sometimes becomes competent after a subtotal cystectomy and substitution cystoplasty irrespective of the original type of bladder dysfunction and irrespective of subsequent cystoplasty behaviour. Equally, a distal sphincter which is only marginally obstructive may become markedly obstructive when an artificial sphincter cuff is wrapped around it, even when the cuff itself is not constrictive.

These observations have therapeutic implications. Firstly, as dyssynergic bladder neck obstruction is never seen, bladder neck incision or resection is never indicated for the relief of outflow obstruction in children with congenital cord lesions who have contractile bladders. Indeed, in half of the group a bladder neck incision would be pointless because the bladder neck is already incompetent and in the other half it will destroy the only normally functioning sphincter mechanism with obvious implications when subsequent relief of the obstruction by endoscopic sphincterotomy is correctly achieved. Secondly, it must not be assumed that an incompetent bladder neck will remain incompetent after a subtotal cystectomy and substitution cystoplasty. Thirdly, a grossly incompetent distal sphincter may become obstructive after an artificial sphincter cuff has been wrapped around it, however loosely. For both of the latter reasons it is advisable to ablate both sphincter mechanisms routinely prior to surgical reconstruction of the lower urinary tract in such children (Mundy and Stephenson, 1984), unless it is intended that the child shall empty the bladder after reconstruction by intermittent self-catheterisation (Stephenson and Mundy, 1985).

These observations also have more theoretical implications. The regular occurrence of bladder neck incompetence and the absence of dyssynergic bladder neck obstruction in children with congenital cord lesions would suggest that dyssynergic bladder neck obstruction in otherwise normal individuals is not neurologically mediated unless it involves some neural mechanism peculiar to that condition.

As an incompetent bladder neck may become competent after subtotal cystectomy, it is unlikely that the incompetence was due to loss of sympathetic activity, as has been suggested (McGuire, 1984), since a loss of sympathetic activity would not be restored by a cystectomy. It seems more likely that bladder neck incompetence is due either to a positive neurally-mediated effect such as a vesico-vesical reflex which is interrupted by subtotal cystectomy to restore bladder neck competence, or it is more simply due to some non-neurological mechanism such as tension in the bladder wall around the bladder neck. As the only children in this study who had competent bladder necks were those with detrusor contractions of normal or increased amplitude that were adequately sustained, and as bladder neck incompetence was just as common in low pressure acontractile bladders at low volume (conceptually those with low bladder wall tension) as in poorly compliant intermediate bladders at maximum capacity (conceptually those with higher bladder wall tension), it seems more likely that competence of the bladder neck is associated with normal or near normal detrusor contractile activity rather than with bladder wall tension. Thus one might argue that bladder neck competence is more related to parasympathetic nerve activity than to sympathetic nerve activity, although there may of course be more than one factor involved.

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The Authors

A. R. Mundy, MS, FRCS, MRCP, Senior Lecturer in Urology and Consultant Urological Surgeon.
P. J. R. Shah, FRCS, Senior Registrar in Urology.
M. Borzyskowski, MRCP, Development Paediatrician.
H. M. Saxton, FRCP, FFR, Consultant Radiologist.

Requests for reprints to: A. R. Mundy, Department of Urology, Guy's Hospital, London SE1 9RT.

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Micturition Disturbance in Parkinson's Disease

HELEN FITZMAURICE, C. J. FOWLER, D. RICKARDS, R. S. KIRBY, N. P. QUINN,
C. D. MARSDEN, E. J. G. MILROY and R. T. TURNER-WARWICK

Departments of Urology and Neurology, The Middlesex Hospital; Department of Neurology, King's College Hospital, London

Summary—Ten men with longstanding idiopathic Parkinson's disease (IPD) were investigated by urodynamic and electromyographic methods. The urodynamic studies were repeated after stopping anti-Parkinsonian medication for several hours. All patients showed a difference between the two studies, but the changes were unpredictable.

Three patients who had high residual urine volumes in both studies were thought to have prostatic obstruction.

EMG analysis showed no evidence of a lower motor neurone lesion affecting the striated urethral sphincter.

It was concluded that micturition difficulty in the patient with IPD is due to detrusor hyperreflexia, influenced by the basal ganglia, which is not associated with impaired striated urethral sphincter activity.

Many patients with Parkinson's disease suffer with urinary symptoms, and the incidence of involuntary detrusor contractions occurring during cystometry is high (Andersen and Bradley, 1976; Pavlakis *et al.*, 1983). In men, there is no satisfactory method of distinguishing between detrusor hyperreflexia and instability secondary to urinary outflow obstruction; the usual urodynamic criteria of obstruction are inapplicable owing to the small volumes of urine passed, and consequently it is difficult to select those patients who might benefit from a prostatectomy.

Outflow obstruction in these patients may be due either to prostatic obstruction or to distal urethral sphincter dysfunction. Previous studies have suggested that there may be a disorder of sphincter relaxation, analogous to the bradykinesia of skeletal muscle, which causes a delay in the initiation of micturition (Raz, 1976; Galloway, 1983; Pavlakis *et al.*, 1983), and the underlying mechanism has been thought to be neuronal degeneration in the corticospinal tract (Andersen and Bradley, 1976). However, recent work has shown that there is no evidence of interruption of the corticospinal pathways to the limbs in IPD (Dick *et al.*, 1984) and it would therefore seem likely that the corticospinal connections to the urethral sphincter are also intact. Analysis of individual motor units from the striated urethral sphincter (Fowler *et al.*, 1984) has enabled us to examine this muscle in greater detail.

The neurological mechanisms leading to detrusor hyperreflexia in IPD are poorly understood. However, Lewin *et al.* (1967) have shown that basal ganglia stimulation in cats results in inhibition of spontaneous detrusor activity. On this basis, administration of levodopa might be expected to reduce detrusor hyperreflexia in patients with IPD, and by studying patients on and off their medication, using urodynamic techniques, we have attempted to test this hypothesis.

Patients and Methods

Ten men in whom a definite diagnosis of IPD had been made were studied. All patients had long-

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standing disease (average time interval since diagnosis was 11 years) and all were receiving levodopa preparations (nine in combination with a peripheral decarboxylase inhibitor), with good clinical benefit. Six patients were taking additional anti-Parkinsonian medication, of whom three were receiving anti-cholinergic drugs (patients 2, 6 and 7 in Table 2). Vagal autonomic function tests of treatment were abnornal in two patients who had complained of postural hypotensive symptoms while on treatment. Two further patients had diabetes mellitus, which was well controlled on diet, with no evidence of peripheral neuropathy.

The age range of the patients studied was 36 to 74 years (mean 59.4). All except one patient had significant urinary symptoms (Table 1), which tended to be worse at night, when the effects of anti-Parkinsonian medication are low.

Table 1

Urinary symptoms	*No. of patients*
Urgency and urge incontinence	3
Hesitancy and poor stream	2
Combination	3
Acute retention	1
None	1

Medium-fill liquid cystometry and voiding studies with simultaneous fluoroscopy were carried out using urethral catheters. Each patient was studied twice: once when on levodopa and on a second occasion after stopping therapy for several hours. EMG studies were carried out in six patients using a concentric needle electrode in the distal urethral sphincter, with analysis of individual motor units as previously described (Fowler *et al.*, 1984), and a total of 60 motor units were analysed.

A control group of normal volunteers underwent urethral sphincter EMG studies. There were eight males and two females with an age range of 23 to 69 years (mean 53).

Results

Urodynamic results are shown in Table 2.

Cystometrography (CMG) revealed a high incidence of detrusor hyperreflexia which, when present, varied in degree between the two studies. The degree of hyperreflexia for an individual patient was considered to be worse in the study in which unstable contractions occurred at a lower volume and/or with a higher maximum detrusor pressure (shown as H +).

All patients with hyperreflexia voided involuntarily as a result of an unstable contraction.

Only one patient (number 4) had stable CMGs in both studies, although the maximum detrusor pressure was higher in the second study.

One patient (number 7) had a hyperreflexic detrusor in the first study, which converted to normal after withdrawal of levodopa (Fig. 1).

Of the eight patients who were hyperreflexic in both studies, five were worse on drugs and three were worse off drugs (Fig. 2).

Peak urinary flow rates were generally very low and did not vary predictably with variation in maximum detrusor pressure. However, three patients were considered to have prostatic obstruction (numbers 2, 9, and 10). These patients all had significant urine volumes on both studies and all had fluoroscopic narrowing of the prostatic urethra. One patient has undergone prostatectomy with symptomatic relief. Post-operatively his CMG was normal.

Urethral sphincter EMG studies in the Parkinsonian patients showed normal motor units with no evidence of reinnervation, including the two with impaired cardiovascular reflexes (Fig. 3). Amplitude and duration of the motor units were similar to those observed in the control group (Fig. 4).)

Fluoroscopic observation of the distal sphincter during voiding showed no evidence of delay in relaxation of this area at the start of, or during micturition, and the appearances were unchanged after levodopa withdrawal.

Discussion

There are many pitfalls in the urological investigation of patients with Parkinson's disease. One problem is the difficulty of diagnosis of IPD. It is now realised that many patients with the clinical syndrome of "Parkinsonism" may have other conditions, *e.g.* multiple system atrophy or progressive supranuclear palsy, and earlier studies may have included patients with these disorders.

In the present investigation we studied patients with Parkinsonism, responsive to levodopa and with no other neurological deficit.

Urinary outflow obstruction is difficult to diagnose in IPD, but may coexist with detrusor hyperreflexia. We suggest that those patients who empty their bladders completely both on and off treatment probably have no evidence of obstruction, despite high maximum detrusor pressures with low

Table 2 Urodynamic Results

		On Levodopa					*Off Levodopa*				
Patient No.	*Age (years)*	*CMG*	*Capacity (ml)*	*Maximum detrusor pressure (cm H_2O)*	*Maximum flow (ml/s)*	*Residual urine (ml)*	*CMG*	*Capacity (ml)*	*Maximum detrusor pressure (cm H_2O)*	*Maximum flow (ml/s)*	*Residual urine (ml)*
1	75	H	100	70	5	50	H+	250	110	10	0
2	71	H	200	50	5	175	H+	100	120	20	80
3	59	H+	100	250	10	0	H	250	100	15	0
4	42	N	430	30	26	0	N	400	80	20	0
5	61	H+	250	100	10	0	H	300	40	10	0
6	58	H+	250	50	10	0	H	400	50	10	0
7	36	H	400	60	20	0	N	500	25	25	0
8	68	H+	300	100	20	0	H	400	50	15	0
9	64	H+	250	60	0	200	H	100	40	0	100
10	62	H	350	150	15	100	H+	150	140	20	100

Key: H = Hyperreflexic N = Normal.

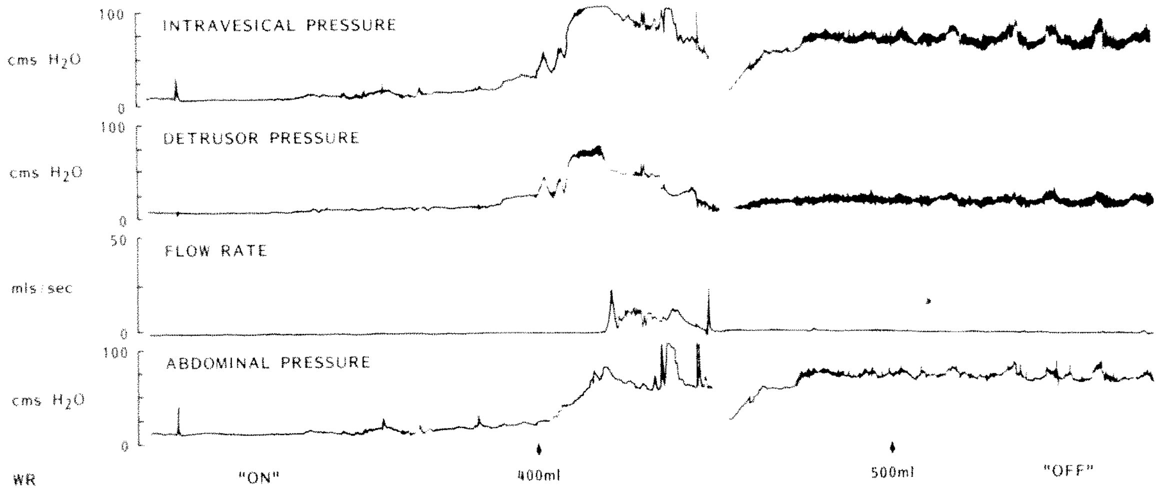

Fig. 1 Cystometrogram showing detrusor hyperreflexia on drugs, converting to normal off drugs. (Note the increase in tremor off drugs).

flow rates. However, three of our patients had high residual urine volumes in both studies, together with prostatic urethral narrowing on fluoroscopy, and therefore have presumptive evidence of prostatic obstruction. We were unable to confirm the suggestion of Galloway (1983) that obstruction in Parkinson's disease occurs at the level of the striated sphincter, as our fluoroscopic studies showed normal relaxation of this area both on and off treatment. Furthermore, our EMG analysis has shown no evidence of a lower motor neurone lesion affecting the striated urethral sphincter in IPD.

We have also demonstrated that levodopa has a marked but variable effect on bladder activity. Sometimes levodopa appears to decrease the degree of detrusor hyperreflexia (as in three of our patients) but in others it appears to make the detrusor more hyperreflexic (in six patients).

It is difficult to decide how levodopa alters bladder function. The most obvious explanation is that through metabolism of dopamine in the brain, levodopa alters striatal dopaminergic function. However, dopamine pathways and receptors exist elsewhere, in the cerebral cortex, diencephalon, and even in the spinal cord. We cannot exclude an action of levodopa or its metabolites upon the bladder itself, although the latter is not known to contain dopamine receptors. Levodopa can be converted, via dopamine, to noradrenaline, but this is unlikely to have occurred outside the central

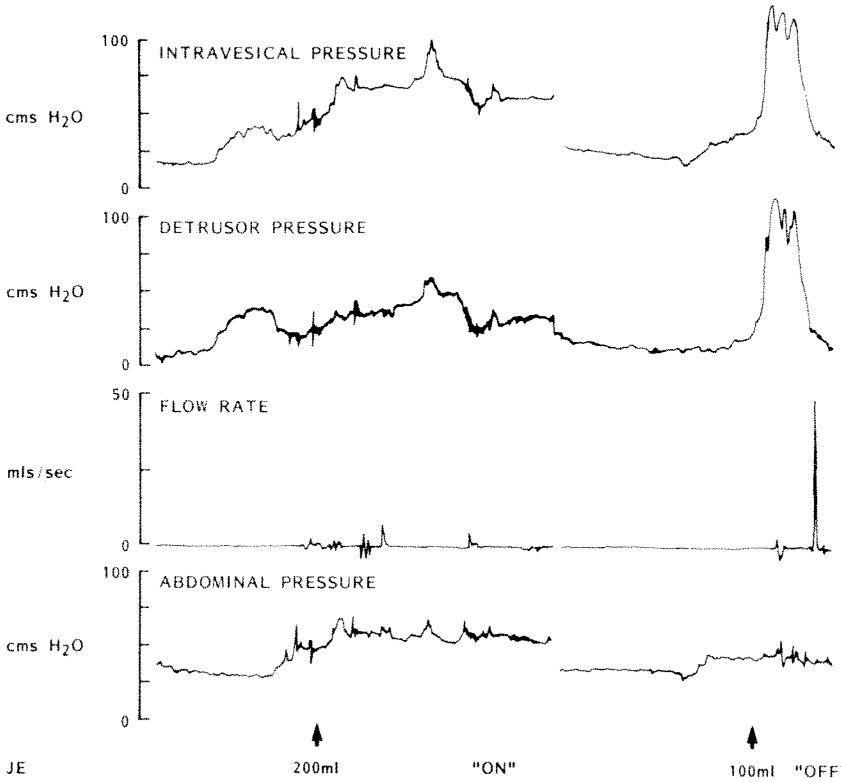

Fig. 2 Cystometrogram showing detrusor hyperreflexia in both studies, worse after stopping drugs.

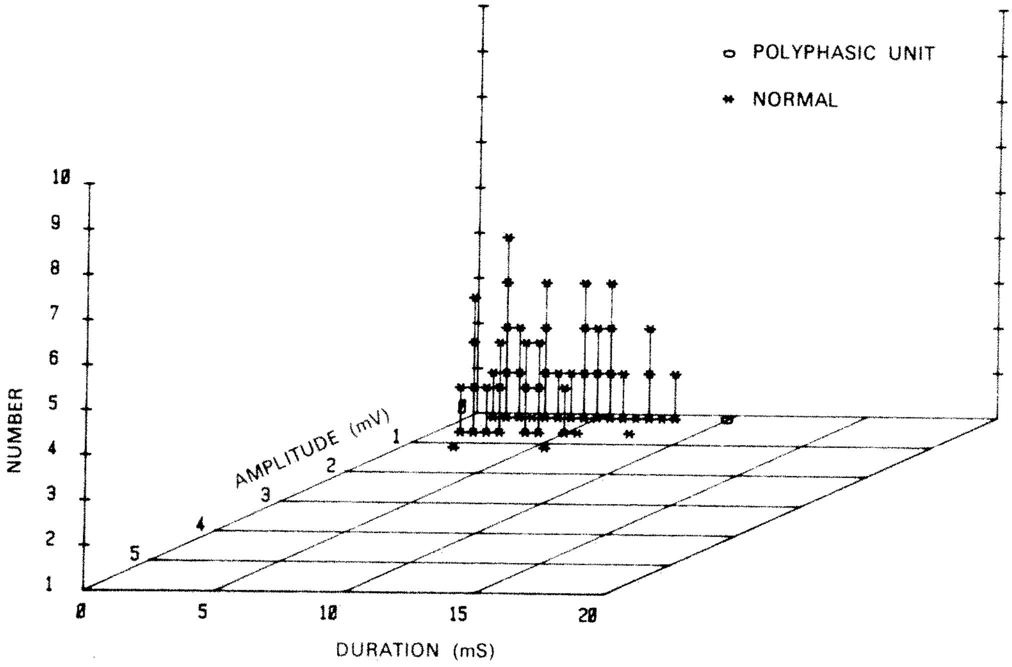

Fig. 3 A 3-dimensional histogram showing the distribution of motor units for amplitude and duration, recorded from six patients with Parkinson's disease.

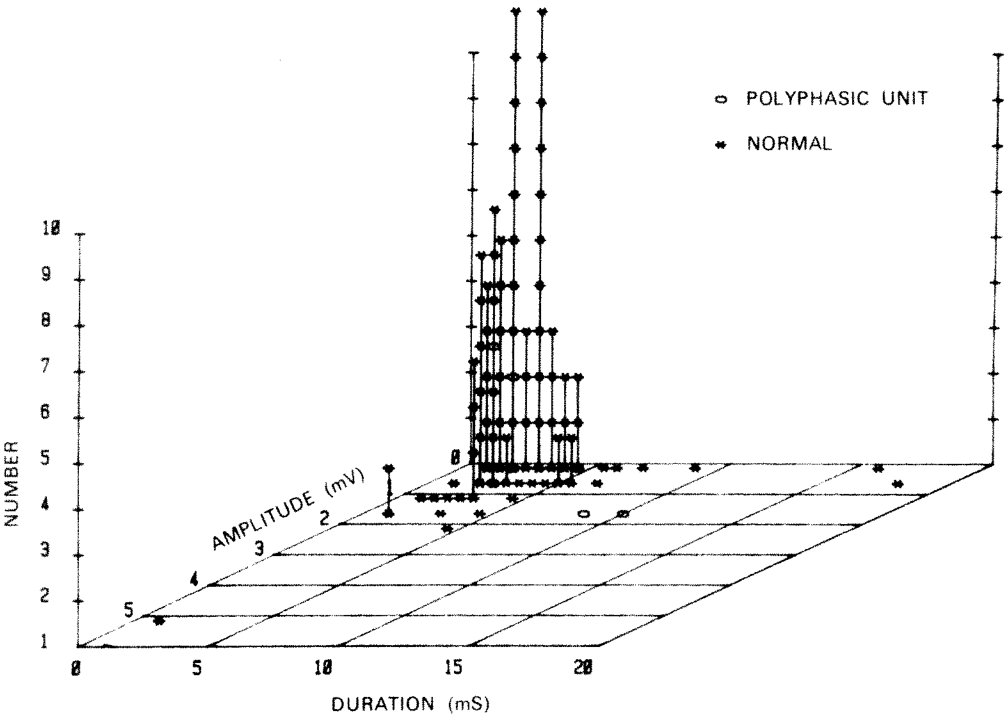

Fig. 4 A 3-dimensional histogram showing the distribution of motor units for amplitude and duration recorded from control subjects.

nervous system in our patients, as all were taking additional peripheral decarboxylase inhibitors.

In conclusion, it seems most likely that the striatum does exert some control over the bladder, and that in the majority of patients with Parkinson's disease striatal dopamine depletion leads to detrusor hyperreflexia, although careful urodynamic study has identified a small group of patients in whom prostatectomy may be beneficial. Why levodopa replacement therapy sometimes improves hyperreflexia, and sometimes makes it worse, is not clear.

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The Authors

H. Fitzmaurice, FRCS, Research Registrar, Department of Urology, The Middlesex Hospital.

C. J. Fowler, MRCP, Senior Registrar, Department of Neurology, The Middlesex Hospital.

D. Rickards, FRCR, Consultant, Department of Radiology, The Middlesex Hospital.

R. S. Kirby, FRCS, Senior Registrar, Department of Urology, The Middlesex Hospital.

N. P. Quinn, MRCP, Lecturer, Department of Neurology, King's College Hospital.

C. D. Marsden, MRCP, Professor, Department of Neurology, King's College Hospital.

E. J. G. Milroy, FRCS, Consultant Urologist, The Middlesex Hospital.

R. T. Turner-Warwick, DM(Oxon), MChir, FRCP, FRCS, FACS, Consultant Urologist, The Middlesex Hospital.

Requests for reprints to: Miss Helen Fitzmaurice, FRCS, Department of Urology, The Middlesex Hospital, Mortimer Street, London W1N 8AA.

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A Double-blind Controlled Trial of a New α-1 Blocking Drug in the Treatment of Bladder Outflow Obstruction

J. W. A. RAMSAY, G. I. SCOTT and H. N. WHITFIELD

Department of Urology, St Bartholomew's Hospital, London

Summary—Thirty-one patients with urodynamically proven bladder outflow obstruction were treated with Alfuzosin in a 3-month, double-blind, placebo-controlled study. The irritative symptoms of bladder outflow obstruction were improved significantly in the treatment group, according to both objective and subjective evaluation. There was no objective evidence of a reduction in outflow resistance or obstruction in either group.

Patients with bladder outflow obstruction due to benign prostatic hypertrophy (BPH) require a transurethral resection. Some of these patients will join a waiting list for operation and a smaller number may be unwilling or unfit for surgery. A drug which ameliorated the symptoms ascribed to prostatism without inducing side effects would be of clinical benefit to these patients provided that it did not prejudice bladder function. A selective α-blocking drug might be expected to fulfil these criteria. This double-blind controlled trial aimed to define the urodynamic effects of a new selective α-blocking drug (Alfuzosin) which has been shown to be of symptomatic benefit to patients with BPH in open trials.

Patients and Methods

Thirty-one patients were allocated into one placebo group and two treatment groups (Table). The diagnosis of bladder outflow obstruction was confirmed by a video pressure cystogram, a urethral pressure profile (UPP) by the Brown and Wickham technique and by measurement of urinary flow rate. Bladder neck dyssynergia was present in three patients and BPH was diagnosed in the remaining 28. Patients with concurrent medical disorders and those who were taking medication which affected the automatic nervous system were excluded. All patients were assessed at monthly intervals by a symptomatic enquiry complemented by urinary flow rate estimation. At the end of the third month the urodynamic studies were repeated. Three patients withdrew from the study for reasons unrelated to the inclusion criteria; two patients developed jaundice (due to gallstones in one and Gilbert's syndrome in another) and one patient developed mild hypercalcaemia which was proven to be due to hyperparathyroidism.

Table Demographic Details of Patients

	Alfuzosin 3 mg tds	*Alfuzosin 4 mg tds*	*Placebo*
Number	10	10	11
Age (mean)	52.9	51.1	60.9
Age (range)	24-62	30-66	47-71
Diagnosis	9 BPH 1 Dyssynergia	8 BPH 2 Dyssynergia	11 BPH

Results

The most significant finding was an improvement in the frequency of micturition ($P=0.039$) (Fig. 1). There was no change in urinary flow rate and no significant difference in the height or the length of the UPP. The end filling pressures and the voiding

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

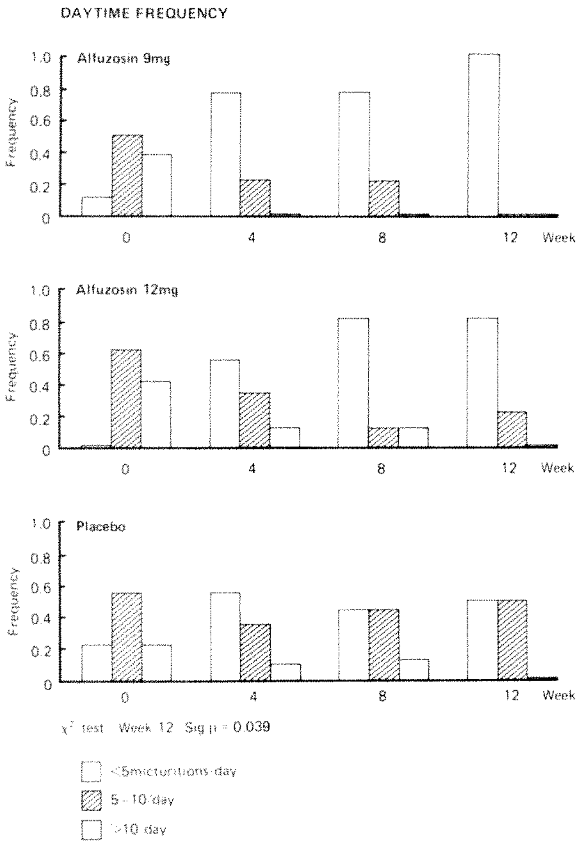

Fig. 1 Symptomatic assessment.

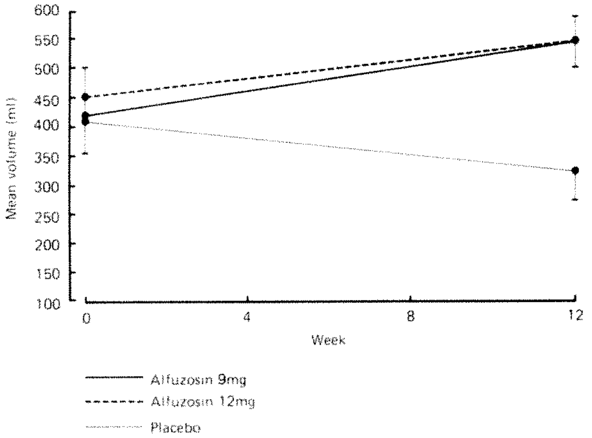

Fig. 2 Objective assessment—volume producing a strong desire to void.

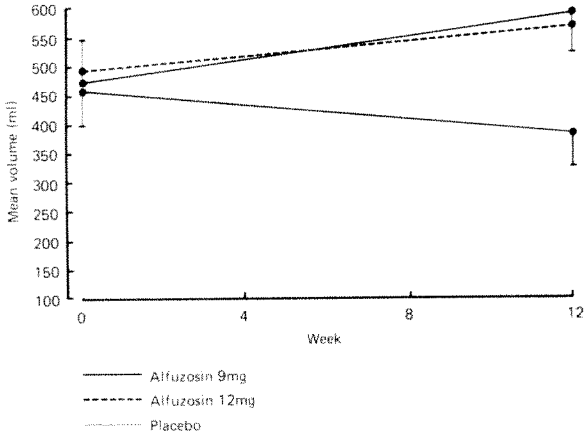

Fig. 3 Objective assessment—total volume voided.

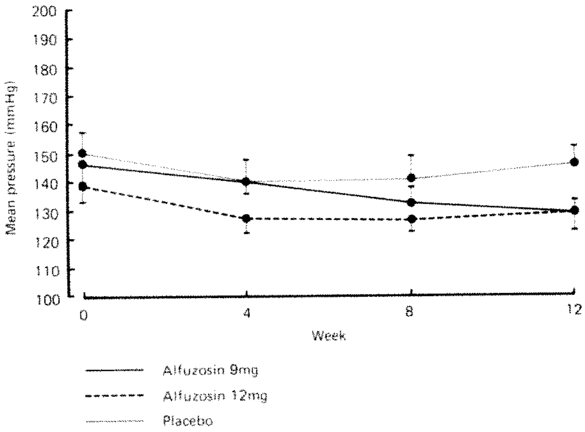

Fig. 4 Objective assessment—measurement of standing systolic blood pressure.

pressures were constant in all groups. Bladder instablity initially present in five cases did not alter significantly. Residual urine volume showed no significant change but there was a significant increase in the volume producing a strong desire to void (Fig. 2) which was reflected by a significant increase in the total volume voided (Fig. 3) in the treatment groups.

No patient withdrew from the trial because of side effects. However, two patients reported diarrhoea which occurred only on the first day of treatment and one patient complained of headache during the first week of treatment.

There was a small decrease in systolic blood pressure (Fig. 4) but no symptoms were reported which could be attributed to postural hypotension.

Discussion

Phenoxybenzamine (PBZ) is effective in reducing bladder outflow resistance and in improving the symptoms of bladder outflow obstruction (Abrams *et al.*, 1982). Dizziness associated with postural

hypotension limits the use of PBZ in some patients. PBZ blocks both α-1 and α-2 adrenergic receptors; Alfuzosin is a selective α-1 blocker and is similar to Prazosin in this respect. Selective α-1 blocking agents should have minimal cardiovascular effects in normotensive subjects and this was confirmed by Alfuzosin. Prazosin has been associated with severe first-dose hypotension. This effect was not evident with Alfuzosin. Alfuzosin produced a reduction in the irritative symptoms of bladder outflow obstruction; Perlberg and Caine (1982) noted that the normal beta response of the detrusor to sympathetic stimulation was transformed to an α contractile response in some cases of prostatic obstruction. A similar change in detrusor sympathetic receptors in the patients in this study would explain both the objective and subjective improvements described.
tive improvements described.

Alpha-one receptors are also found in the bladder trigone. The effects of selective α-1 blockade induced by Alfuzosin may also be explained by a reduction in the response of these receptors to the stretch induced by bladder filling.

Alfuzosin improves the irritative symptoms of bladder outflow obstruction without causing unwanted urological or generalised side effects. It may be useful in the treatment of patients awaiting prostatectomy, particularly if they also require hypotensive medication.

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The Authors

J. W. A. Ramsay, FRCS, Research Registrar.
G. I. Scott, MB, BS, Research Registrar.
H. N. Whitfield, MA, MChir, FRCS, Consultant Urologist.

Requests for reprints to: J. W. A. Ramsay, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Improved Presentation of Data in a Urodynamics Clinic by Use of a Microcomputer

A. J. CRAWFORD and JENNY WALKER

Medical Physics Department, Queen's Medical Centre, and Genitourinary Unit, City Hospital, Nottingham

Summary—A microcomputer system is described for the collection, analysis and printing of the physiological data gathered during a urodynamic investigation. Examples are given of the results obtained from such a system.

Physiological data in a urodynamics clinic are traditionally presented on a multi-channel chart recorder; the quality of the traces is often poor and the amount of paper generated during the filling and voiding sequences may be prodigious. This can make the task of the clinician more difficult, both in the interpretation of the data and in the storage of the paperwork. A low cost microcomputer system has been assembled to present the data in a form which can be readily assimilated. The equipment comprises a BBC microcomputer, television monitor, printer and disc drive.

Materials and Methods

The BBC microcomputer is equipped with four analogue-to-digital converters, each of which can sample and record one channel of information. When all four channels are used, as in this application, the maximum sampling rate is one sample per channel every 0.04 s with an accuracy rate exceeding 0.5%. For urodynamic signals, which are comparatively slow-moving, an adequate sample rate is one sample per channel every 0.2 s. However, we have found that the effective sample rate may be further reduced by averaging five consecutive samples to give an overall rate of one sample per second for each channel; this improves the clarity of the data without excessive loss of detail.

The inputs to the computer are connected in parallel to those feeding the chart recorder or other device displaying the amplified electrical signals from the physiological transducers. The maximum voltage that the computer can accept is 1.8 volts; the level of amplification should therefore be adjusted so that this voltage is not exceeded when the physiological measurements reach their maximum expected values.

In the filling phase, the four channels sampled are the total bladder pressure, rectal pressure, filling volume and an "event" signal which may be used to indicate either cough or sensation levels. At the start of the investigation, patient details are typed into the computer and a designated key is pressed to initiate the collection of the filling data. Upon completion of filling, the same key is again pressed; the computer then calculates the detrusor pressure values by subtracting the rectal pressures from the corresponding total bladder pressure values and transfers all of the collected information on to floppy disc for storage. The computer then switches to its voiding mode and awaits the onset of micturition.

When the computer detects that voiding has commenced, it starts to record the total bladder pressure and the rectal pressure together with the voided volume and the flow rate. Data collection ceases either when the flow rate remains at zero for a pre-determined period of time or, if preferred, when a designated key is pressed on the computer. At this point, the detrusor pressures are calculated as before and the data again transferred on to

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Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

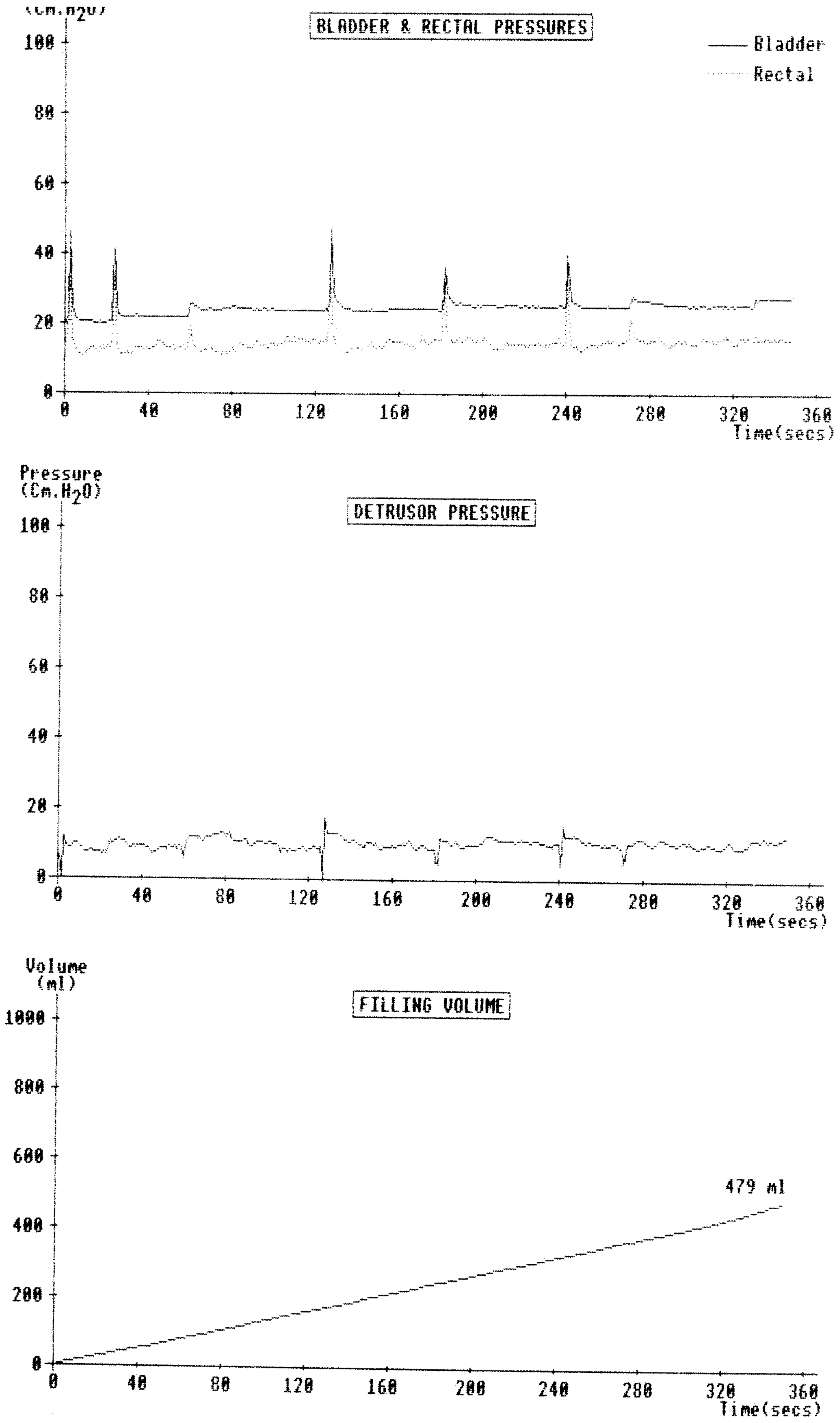

Fig. 1 Print-out of filling phase.

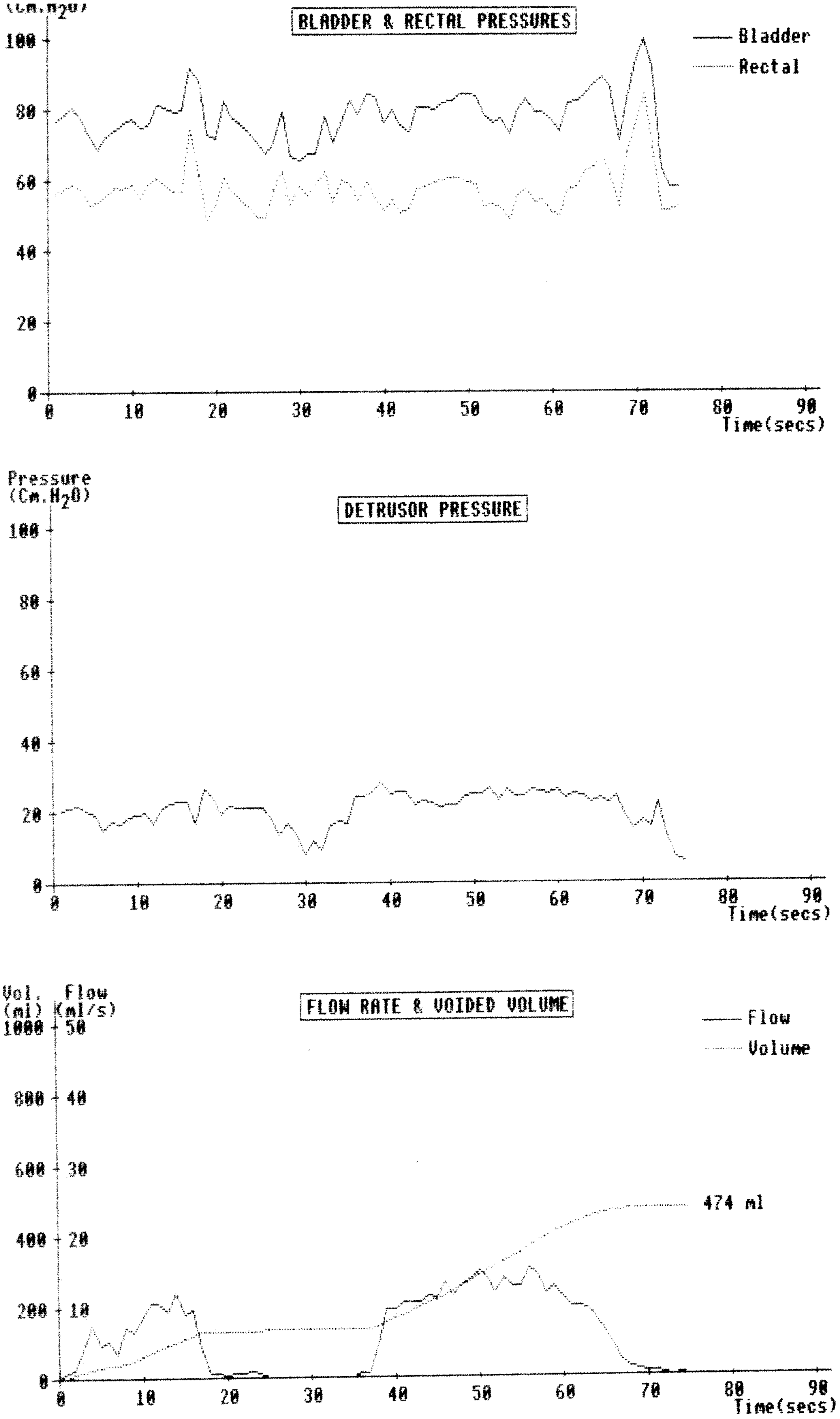

Fig. 2 Print-out of voiding phase.

floppy disc to form a complete record of the filling and voiding parameters for that patient.

Results and Discussion

At the end of the clinical session, or after each patient if desired, the computer provides a printout of the filling and voiding data for each patient in graphical form. The scales on the axes of the graphs are automatically selected for optimum display of the data. A sample print-out of the filling sequence data is given in Figure 1 and for the voiding sequence data in Figure 2. The format of the print-outs may readily be changed to fulfil the needs of a particular clinician.

Further information may be derived from the physiological data stored on the floppy disc. For example, the detrusor shortening velocity (Griffiths, 1980) can be calculated and plotted against detrusor pressure if required. Useful parameters which may be printed on the graphs, or on a separate sheet of paper, include peak flow rate, mean flow rate, voiding time and time-to-peak flow, amongst others. The programming of the computer is in the BASIC language and can easily be re-written to suit most requirements.

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The Authors

A. J. Crawford, BSc, PhD, CEng, Principal Physicist, Queen's Medical Centre.

Jenny Walker, FRCS, Senior Surgical Registrar, Alder Hey Children's Hospital, Liverpool.

Requests for reprints to: A. J. Crawford, Medical Physics Department, Queen's Medical Centre, Nottingham NG7 2UH.

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Oncogenes and Bladder Cancer

P. R. MALONE, K. V. VISVANATHAN, B. A. J. PONDER, R. J. SHEARER and
I. C. SUMMERHAYES

Institute of Cancer Research, Royal Marsden Hospital, London

Summary—We screened a series of 15 superficial and invasive transitional cell carcinomas of the bladder for transforming activity on the NIH/3T3 transfection assay. In addition, by obtaining tumour DNA and normal lymphocyte DNA from the same patients we looked for evidence of gene amplification or rearrangement of the c-H-*ras*-1 gene by Southern blot analysis.

One patient (with a grade 2 T1 tumour) was shown to have an activated oncogene on the NIH/3T3 transfection assay and this was identified as a c-H-*ras*-1 gene. We could find no evidence of gene amplification or rearrangement of this gene in any tumour.

The significance of activation of *ras* oncogenes in the pathogenesis of human bladder carcinoma is unclear.

Transformation of NIH 3T3 cells by DNA extracted from human tumours has now been widely used as an assay to identify transforming genes (Marshall, 1985). The "oncogenes" identified by this method have mainly belonged to the *ras* gene family and specifically in bladder carcinoma H-*ras*-1 has been found most commonly (Fujita *et al.*, 1984). In these cases activation has been shown to be due to a point mutation around positions 12 or 61 in the base coding sequence (Reddy *et al.*, 1982; Tabin *et al.*, 1982; Fujita *et al.*, 1984). However, only about 10% of the bladder tumours analysed to date prove active in the NIH/3T3 transfection assay, and workers studying different malignancies have characterised alternative changes involving oncogenes which may play a role in the genesis of neoplasia in these tissues. These include DNA rearrangements by translocation of the proto-oncogene to a different part in the genome, with the probable loss of the normal controlling influences on the gene (*e.g.* Burkitt's lymphoma) (Erikson *et al.*, 1983) and gene amplification where multiple gene copies are found, leading to increased gene expression (*e.g.* in neuroblastoma) (Brodeur *et al.*, 1984).

We present a study of 15 superficial and invasive bladder tumours tested for transforming activity on the NIH/3T3 transfection assay. In addition, by obtaining tumour DNA and normal lymphocyte DNA from the same patient, we screened for rearrangement and amplification of the H-*ras*-1 gene as an alternative method of activation in these tumours.

Materials and Methods

Details of tumour grade and stage are given in the Table. All were untreated transitional cell carcinomas. All tumours were obtained by transurethral resection and stored in liquid nitrogen. Fifty ml of blood anticoagulated by K^+EDTA were lysed in concentrated sucrose solution, the nuclei extracted by centrifugation and the nuclear pellet stored in

Table Grades and Stages of Tumours Analysed in this Study

Stage	*Ta*	*T1*	*T2*	*T3*	*T4*
Number of patients	3	6	1	3	2
Grade	1	2	3		
Number of patients	4	8	3		

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liquid nitrogen. Thereafter both samples were treated similarly. The samples were thawed and the DNA was purified by extraction against phenol and chloroform. The DNA solution was then stored at 4°C.

NIH/3T3 transfection assay

High molecular weight DNA was transfected into NIH/3T3 cells by calcium phosphate precipitation (Shih *et al.*, 1981). Transformation was judged by both focus formation and also tumourigenicity in nude mice as described by Blair *et al.* (1982). Secondary and tertiary transfectants were obtained by transfection of DNA extracted either from harvested transformed cells in the focus assay or tumours in the second assay. The presence of human DNA in transfected cells was confirmed by Southern blotting with human DNA specific ALU probe. Tertiary transfectants were then screened for c-H-*ras*-1, c-K-*ras*-2, and N-*ras* genes using the same technique.

Southern blotting

Genomic tumour and lymphocyte DNA was digested with EcoR1 and BamH1 restriction endonucleases which cut DNA at specific coding sequences. These enzymes were chosen as they are known to cut outside the H-*ras*-1 gene to produce fragments containing the gene and flanking sequences. Equal amounts of tumour and lymphocyte DNA were loaded on to an 0.6% agarose gel and the restriction fragments separated according to molecular weight by electrophoresis. The DNA was then transferred to nitrocellulose paper essentially as described by Southern (1975). The restriction fragment containing the c-H-*ras*-1 gene was identified by hybridising the nitrocellulose paper with nick-translated probe at 42°C in a buffer containing 50% formamide. The probe used was a 2.9 kilobase (kb) Sst restriction fragment from the cloned c-H-*ras*-1 gene. By making both the blot and probe DNA single stranded they will bind where there is sequence homology. Multiple gene copies will bind more probe and show as a stronger band on the autoradiograph, whereas rearrangement around the gene will alter the cutting pattern of the restriction enzymes and hence the molecular weight of the restriction fragment.

Blots were washed at 60°C in $0.1 \times \text{SSC}/0.1\%\text{SDS}$, and autoradiography was carried out using an intensifying screen at −70°C.

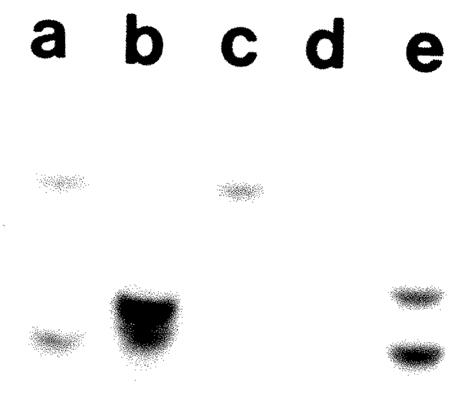

Fig. 1 Southern blot analysis of tertiary transfectants probed with the 2.9 Sst fragment of the c-H-*Ras*-1 gene. Lanes a, c and e represent three separate tertiary transfectants of the same tumour DNA. Lane d is normal NIH/3T3 DNA (Negative control) and lane b is NIH/3T3 pEJ DNA gene (Positive control).

Results

Two patients proved positive on the NIH/3T3 transfection assay. In one case the presence of human repetitive ALU sequences was confirmed in the secondary and tertiary transfections. Tertiary transfectants were then screened with different members of the *ras* family and found to be positive for c-H-*ras*-1 (Fig. 1). Further work using oligonucleotide probes has identified an alteration at the second base of the twelth codon in this gene (data not shown). In the second case no human DNA could be detected in the tertiary transfectant and this may have been a spontaneous transformant.

The cutting of high molecular weight DNA with the restriction enzyme Eco R1 resulted in the c-H-*ras*-1 gene being carried on a 23 kb fragment in all samples studied in Southern blot analysis. No differences in the hybridisation pattern were observed between tumour and lymphocyte DNA, indicating no demonstrable rearrangement in these cases (Fig. 2). In contrast, cutting with Bam H1 resulted in a number of different restriction patterns. However, the restriction fragments observed were of the same size in any one patient studied, showing that no somatic alteration had occurred (Fig. 3). In both digestions the fact that no significant difference in the intensity of hybridisation was observed would

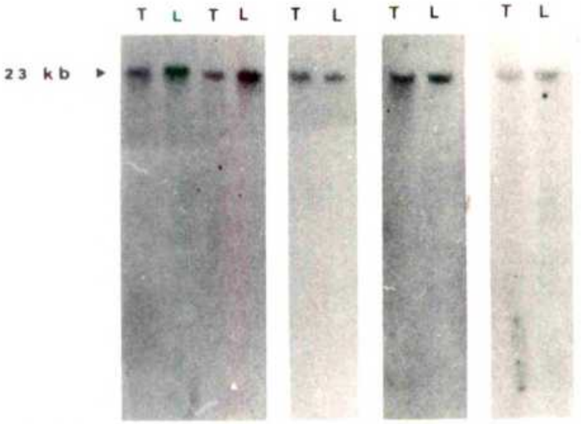

Fig. 2 Pairings of tumour and lymphocyte DNA from the same patient. Southern blot analysis where DNA is cut with Eco R1 and probed on nitrocellulose with the 2.0 kb Sst fragment from the c-H-*ras*-1 gene.

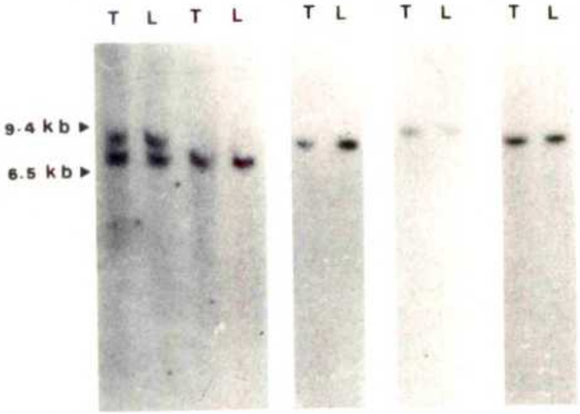

Fig. 3 Pairings of tumour (T) and lymphocyte (L) DNA from the same patient. Southern blot analysis where DNA is cut with Bam H1 and probed on nitrocellulose with the 2.9 Sst fragment from the c-H-*ras*-1 gene. The heterogeneity between individual pairs represents sequence polymorphism around the gene.

indicate no apparent amplification of the c-H-*ras*-1 gene in these cases.

Discussion

The potency of many carcinogens has been shown to be closely related to their ability to mutate DNA (Ames *et al.*, 1973). The argument that such changes are the cause of neoplastic progression has been supported by the recent finding that DNA, extracted from human tumours and active in transforming NIH/3T3 cells, has specific mutations that are responsible for this transformed phenotype. The link between oncogenes and carcinogens has been strengthened by the finding that a normal proto-oncogene can be altered by a chemical carcinogen *in vitro* to produce changes identical to those reported to occur naturally in human tumours (Marshall *et al.*, 1984).

The fact that most oncogenes detected by the NIH/3T3 transfection assay are *ras* genes may reflect an inherent bias in the assay to detect point mutations in these genes. The c-H-*ras*-1 gene is one of five closely related genes, three of which have been shown to be active in the 3T3 transfection assay. These genes are present throughout all phyla studied and code for a very similar 21,000 D protein. The conservation of these genes throughout evolution suggests that they may play a vital role in normal cell growth regulation, and studies involving microinjection of *ras* protein (Feramisco *et al.*, 1984) indicate that they may be involved in the control of cell division.

The role of *ras* genes in the pathogenesis of human bladder cancer is unclear. Our results confirm that only a minority of bladder tumours possess transforming activity on the 3T3 transfection assay, and in this case the tumour was of fairly low grade. Other workers have also found *ras* activation in low grade superficial bladder tumours and *ras* activation would not necessarily appear to be an indicator of poor prognosis.

Increased expression of the *ras* genes at the RNA and protein level has been implicated in human tumours (Slamon *et al.*, 1984; Thor *et al.*, 1984). We have looked at the DNA level and found no evidence of gene amplification or rearrangement of the H-*ras*-1 gene in 15 human bladder tumours (within the limits of the technique of Southern blotting). If increased levels of *ras* protein play a part in neoplastic progression, the altered control would appear to reflect changes at the transcriptional or translational level in the cell.

Our findings are in accordance with those of others—that activated *ras* genes can be detected in about 10% of human bladder tumours—but we have found no evidence that rearrangement or gene amplification of c-H-*ras*-1 is a common event. Whilst the finding that mutations in *ras* genes confer malignant potential to immortal cells in culture is an interesting and potentially exciting discovery, its significance in relation to the development of human bladder carcinoma is not clear.

Acknowledgements

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The Authors

P. R. Malone, FRCS, Clinical Research Fellow.
K. V. Visvanathan, BSc, Graduate student.
B. A. J. Ponder, PhD, MRCP, Honorary Consultant Physician, Royal Marsden Hospital, Fellow of the Cancer Research Campaign.
R. J. Shearer, FRCS, Consultant Urologist.
I. C. Summerhayes, PhD, Research scientist.

Requests for reprints to: P. R. Malone, Institute of Cancer Research, Chester Beatty Laboratories, Royal Marsden Hospital, Fulham Road, London SW3.

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DNA/RNA Ratio in Bladder Cancer: a Factor Indicating the Recurrence Rate?

G. G. HADJISSOTIRIOU, D. K. GREEN, M. A. McINTYRE, T. B. HARGREAVE and
G. D. CHISHOLM

University Department of Surgery/Urology, Department of Pathology and MRC Clinical and Population Cytogenetics Unit, Western General Hospital, Edinburgh

Summary—Flow cytometry (FCM) was used to monitor 24 patients receiving intravesical mitomycin C (MMC) therapy. The patients were selected for MMC therapy because of multiple low stage bladder tumours which had not been cleared by previous endoscopic management. The response to treatment was monitored with cystoscopy, cytology, mucosal biopsies and flow cytometry.

Follow-up was for a minimum of 12 months and 19 patients (79%) remained free of tumour. Four patients developed recurrences 6 months after therapy (16.5%) and one showed no response. There were no partial responders. The flow patterns of the four patients who developed recurrence showed an increased RNA/DNA ratio; this was detected after the third MMC instillation and remained throughout the follow-up period. The patients who did not develop recurrence demonstrated either a 1:1 or decreased RNA/DNA ratio. The increased RNA/DNA ratio appears to precede cystoscopic, urine cytology or biopsy evidence of recurrence. If this is confirmed in a larger series it could be used to select patients at high risk for recurrence who would be suitable for alternative therapy.

Flow cytometry has been used as a method of investigation of bladder cancer for as long as 10 years (Melamed *et al.*, 1976) but it remains a sophisticated technique requiring complex apparatus. This technique measures the DNA and RNA content of a large number of representative cells and gives a profile of their DNA and RNA content. Normally the cells in a bladder washout are a single population of transitional cells containing diploid DNA. The DNA content is exactly the same as in peripheral blood lymphocytes which can be used as a control. RNA exhibits an equally unimodal distribution. Just before cell division each dividing or malignant cell is seen to contain twice as much DNA (tetraploid). There is also a further set of cells about to divide where DNA is being synthesised and this population can be seen in the S region. Figure 1 is a typical flow pattern from cultured normal lymphocytes showing the diploid, tetraploid, and S regions. Thus it is possible from the flow cytometer to measure DNA distribution and therefore to estimate the numbers of dividing cells. The established values (Melamed, 1984) for transitional cell cancer in bladder washout specimens are:

(1) Negative specimens: < 10% cycling cells.
(2) Suspicious specimens: 10-15% cycling cells.
(3) Positive specimens: (a) > 15% cycling cells. (b) Definite tetraploid peaks accounting for more than 10% of the total. (c) Aneuploid peaks.

The purpose of this study was to evaluate flow cytometry as a means of identifying patients destined to develop recurrence and to monitor the response and cell cycle changes in bladder washings before, during and after treatment with MMC.

Patients and Methods

Twenty-four patients (mean age 71 years, m/f = 1/1)

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Table 1 Tumour Distribution According to Stage and Grade Before Treatment

Grade	*Ta*	*Tl*	*Tis*	
Stage				*Total*
G1	7	5		12
G2	5	2		7
G3		3		3
In situ			2	2
Total	12	10	2	24

with multiple bladder tumours which had failed to respond to previous endoscopic management were studied. All tumours had been histologically proven to be low stage (Ta, Tl, Tis) according to the TNM system. Table 1 shows the distribution according to the grade and stage of the tumours before treatment. Once the decision had been taken that the tumour was beyond endoscopic control and intravesical MMC therapy would be commenced, no further definitive endoscopic treatment was performed. Instead, during the first assessment before MMC, biopsies were taken from the largest tumours and from any suspicious areas of the urothelium, but in all cases the tumour bulk was left intact. Cystoscopy was performed before the first, fourth and eighth MMC instillation and 1, 3, 6, and 12 months after treatment. During cystoscopy urine and bladder washings were collected for FCM and cytology and detailed mapping of the bladder tumours was performed.

The treatment regime was 8 weekly instillations of 40 mg MMC in 40 ml distilled water retained in the bladder for 2 h. A catheter was kept in the bladder to ensure complete emptying and to exclude variable exposure to MMC due to other reasons, *e.g.* prostatic enlargement (Devonec *et al.*, 1983). Mitomycin C is minimally toxic or non-toxic when given intravesically (Soloway *et al.*, 1981; Flüchter *et al.*, 1982). Nevertheless, a full biochemical screen and blood count were done before the first, fourth and eighth instillations. Urine bacteriology was also performed at weekly intervals.

The washout specimens were collected by vigorous barbotage of the bladder with 50 ml 0.9% NaCl; 10 ml were sent for cytology along with the urine specimens. The washings and urine for flow cytometry were refrigerated immediately (4 °C) and processed within the next 4 h. They were first centrifuged at 200 × g for 10 min. The supernatant was discarded and the cell pellet was resuspended into Hank's balanced salt solution to a concentration of 1 million cells/ml. The cell suspension was then filtered through a 64 micron nylon mesh to remove cell fragments and clumps of cells which could obstruct the flow. This cell suspension was then stained using the two-step Acridine orange (AO) technique (Darzynkiewicz *et al.*, 1975; Traganos *et al.*, 1977; Collste *et al.*, 1980). This involved mixing 0.2 ml of the cell suspension with 0.4 ml of a detergent solution (0.1% v/v Triton X-100; 0.08 N HCl; 0.15 M NaCl) and 30 s later adding 1.2 ml of AO staining solution (6.0 µg chromatographically purified AO; 10^{-3} M EDTA; 0.15 M NaCl; 0.1 M citrate phosphate buffer at pH 6). The stained sample was then loaded into a specially built computer controlled flow-cytometer (Green and Fantes, 1983). The machine (Fig. 2) consists of a nozzle assembly which produces a 50 micron "in air" flow stream, two independent fluorescence measurement channels placed at 90° to the incident focused laser beam (Spectra-Physics) and a forward light scatter measurement channel. The stained cells flow in single file, intersecting the focused beam of blue 488 nm laser light which is very close to the excitation maximum of AO. Passing though the beam each cell emits a pulse of fluorescence, green when the dye is bound to DNA and red if to RNA. The pulse is detected by appropriate photomultipliers, measured and then displayed on a computer driven visual display unit. Many hundreds of cells per minute can be measured and, typically, 10,000 cells were measured each time. Measurement was made of DNA, RNA, DNA/RNA ratios and occasionally DNA/forward light scatter to exclude clumps of cells and debris.

Results

Nineteen patients had no evidence of tumour 1 year after treatment. Their flow patterns were similar to the series shown in Figure 3. Table 2 is a chart of a typical patient without recurrences as regards cystoscopy, cytology, biopsy and relative DNA and RNA values. Four patients developed recurrences at their 6-month follow-up. These patients were free of visible tumour before their eighth MMC instillation and biopsies and cytology at that time were also negative. Despite there being no evidence of tumour cystoscopically or on cytology, there was a consistent variation in the flow pattern: broader RNA distribution as compared with DNA. The flow pattern 1 month after treatment was inconclusive with respect to DNA but there was an increase in RNA. Each parameter was positive at the 6-month follow-up. None of the four patients exhibited positive tetraploid DNA after

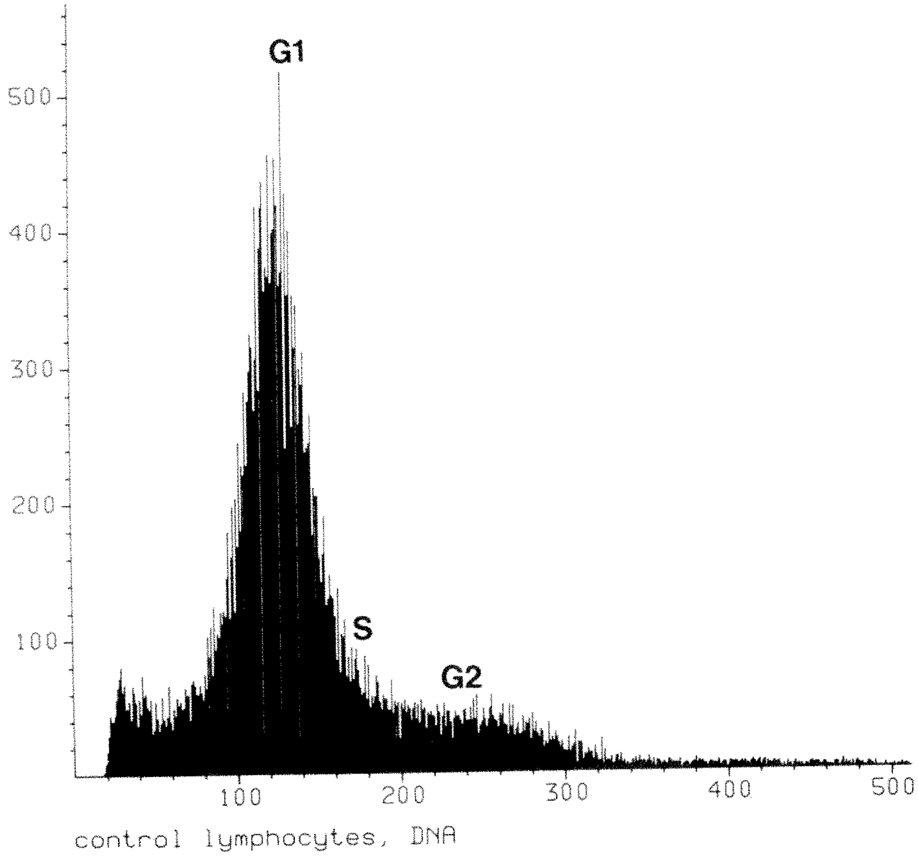


Fig. 1 Flow pattern of control lymphocytes.

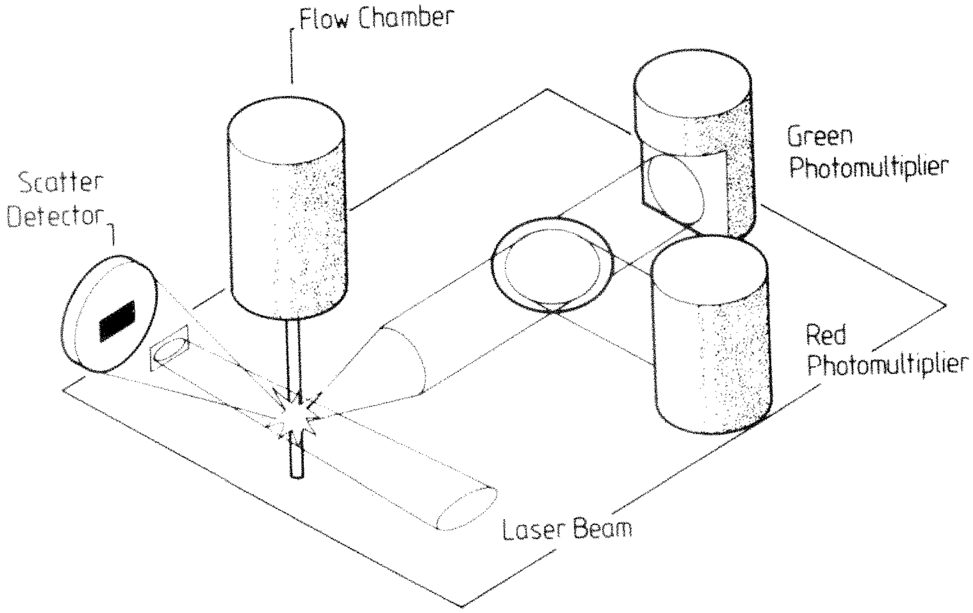
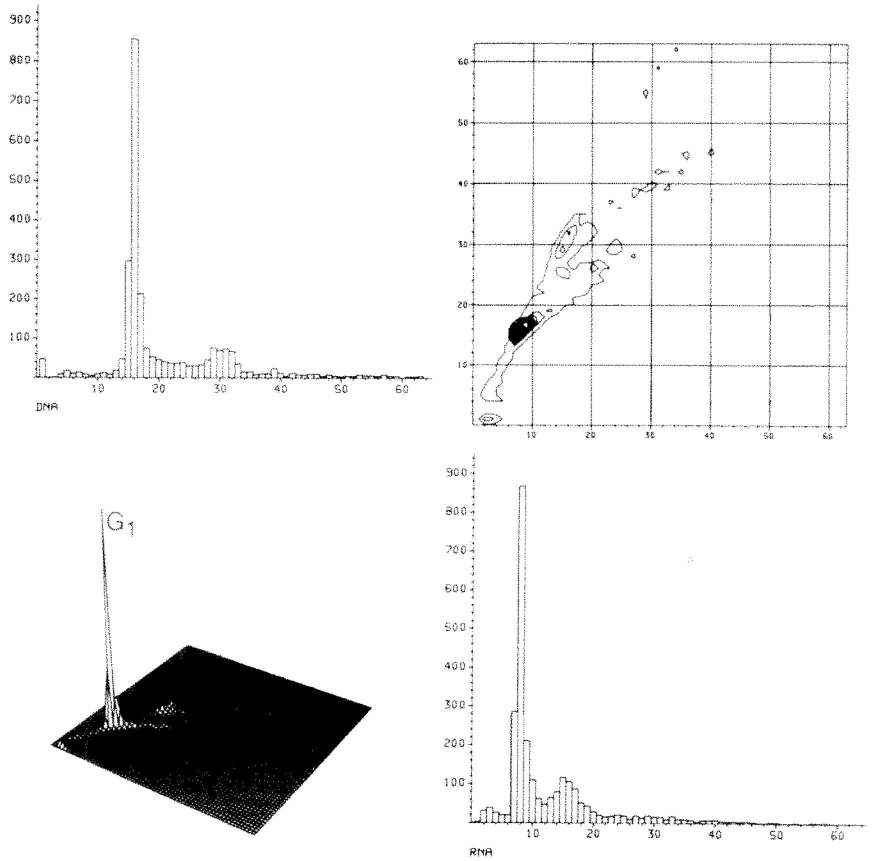


Fig. 2 Basic design of flow cytometer.



900
800
700
600
500
400
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30
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DNA
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1
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Fig. 3A

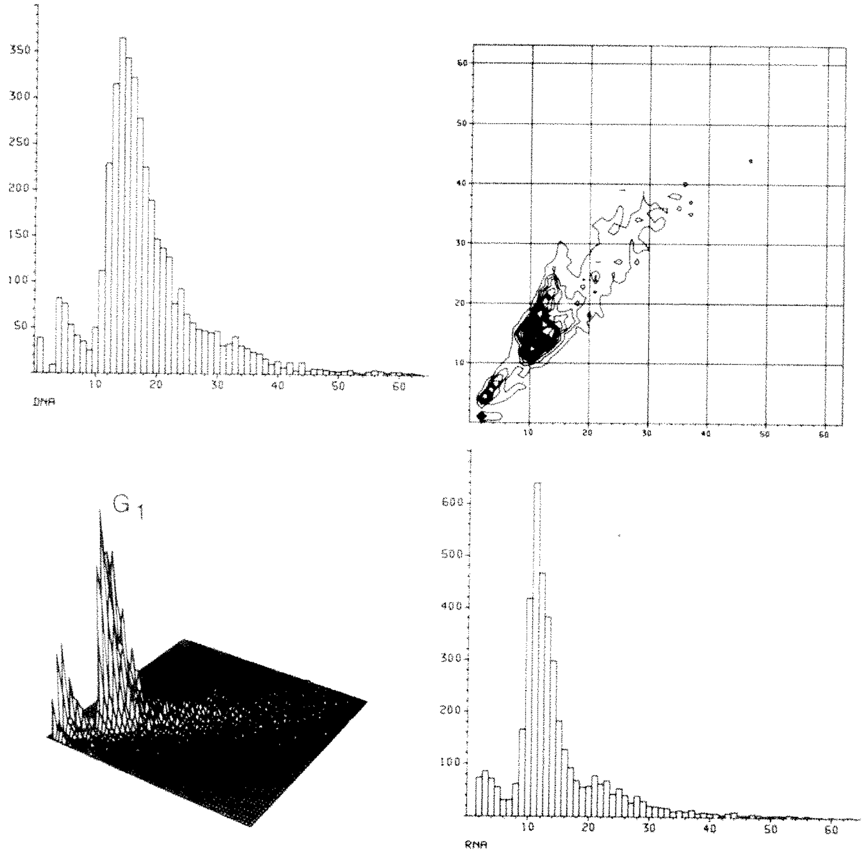

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Fig. 3B

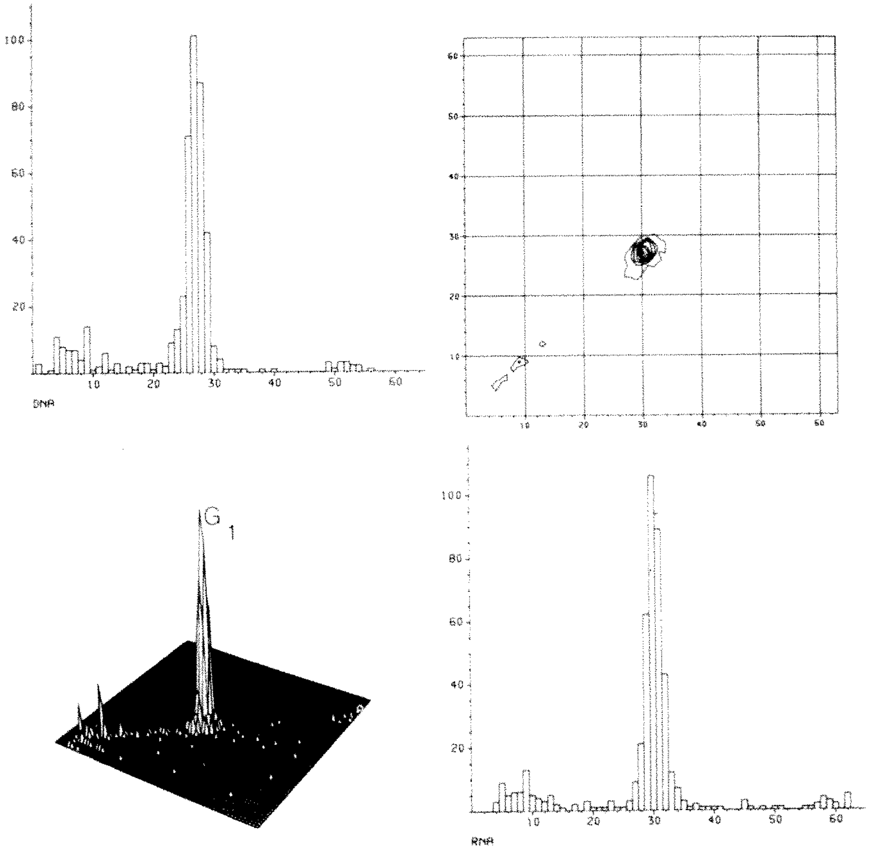


Fig. 3C

Fig. 3 Typical flow patterns (A) before, (B) during, and (C) 1 month after MMC treatment) of patients who did not develop recurrences.

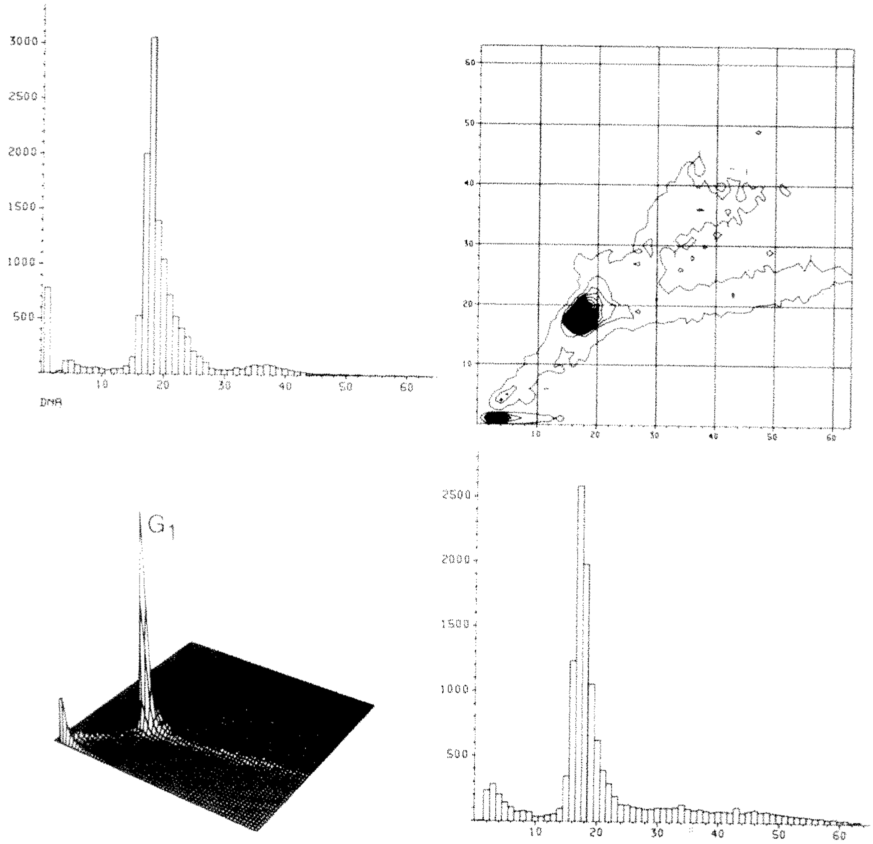
Table 2 Typical Chart of a Patient Without Recurrences

	Cysto	*Cyto*	*BX*	*DNA*	*RNA*
Before					
1st	+	+	+	+	+
4th	+	+	+	− +	− +
8th	−	−	−	−	−
After					
1/12	−	−	−	−	−
3/12	−	−	−	−	−
6/12	−	−	−	−	−
12/12	−	−	−	−	−

treatment. Table 3 is a typical chart of the four patients who developed recurrences and Figure 4 is typical of the flow pattern. Table 4 shows the distribution of recurrent tumours according to their grade and stage before therapy.

Discussion

The purpose of this work was to investigate the use of flow cytometry to monitor mitomycin C intravesical therapy. Patients were not treated with MMC for the purpose of this study but rather the opportunity was taken to study a particularly refractory group of patients who had failed to respond to endoscopic therapy and where intravesical MMC was thought to be the appropriate treatment. Because MMC has the effect of synchronising cell divisions in a normally asynchronous population, it was hoped that the use of flow cytometry might yield new information. MMC is used in several branches of cell biology to synchronise cell populations: when cells are synchronised, monitoring of their cycle and aggressiveness becomes possible. Synchronisation *in vivo* is in many aspects different from that *in vitro*, but we hoped that it might prove a valuable method of monitoring cellular activity in patients receiving intravesical chemotherapy.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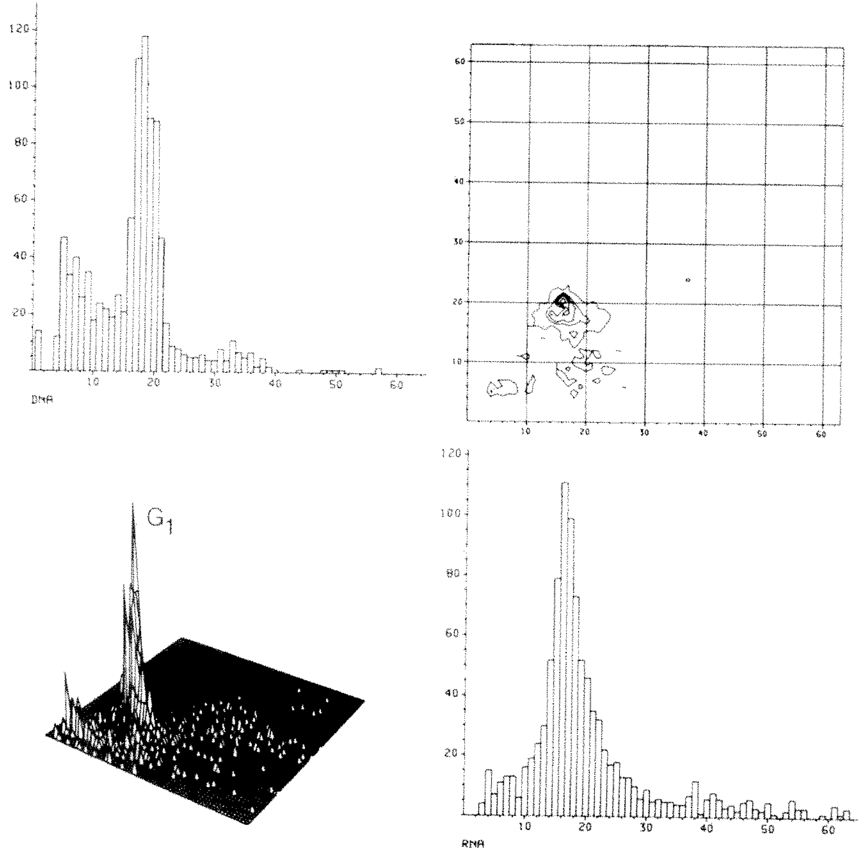
50
60
DNA
G1
RNA

Fig. 4A


120
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DNA
G1
RNA

Fig. 4B

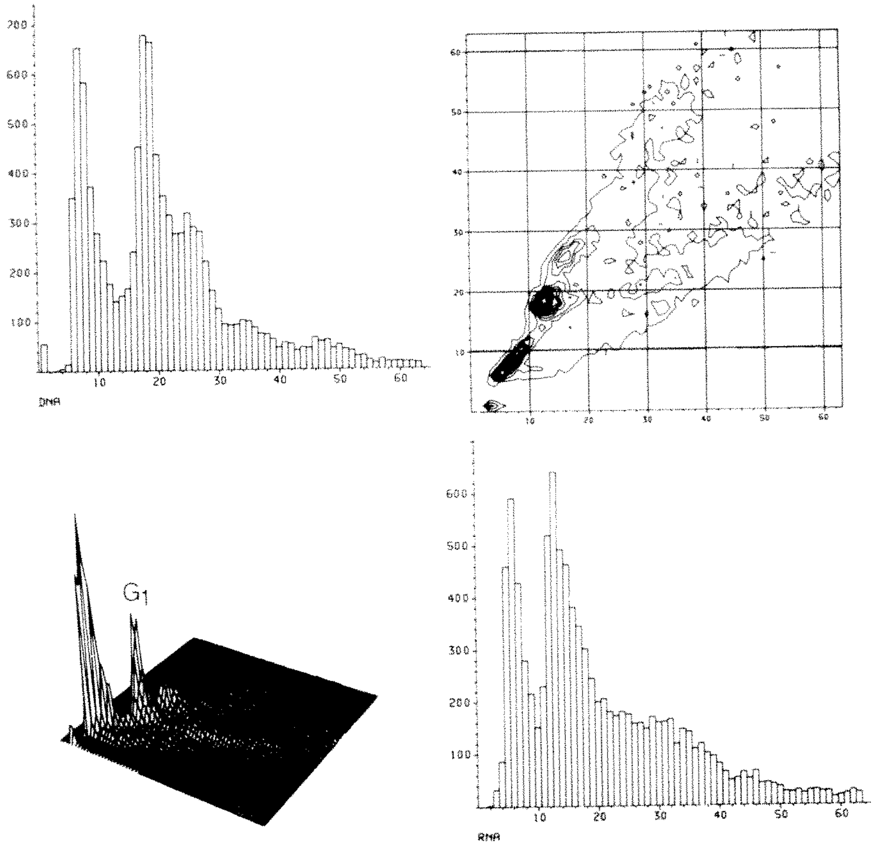

Fig. 4C

Fig. 4 Typical flow patterns (A) before, (B) during, and (C) 6 months after MMC treatment) of patients who developed recurrences.

Table 3 Typical Chart of a Patient Who Developed Recurrences

	Cysto	*Cyto*	*BX*	*DNA*	*RNA*
Before					
1st	+	+	+	+	+
4th	+	+	+	+	+
8th	−	−	−	− +	+
After					
1/12	−	−	−	− +	+
3/12	−	−	−	−	+
6/12	+	+	+	+	+

Table 4 Recurring Tumour Distribution According to Stage and Grade Before Treatment

Grade	*Ta*	*Tl*	*Tis*	
Stage				*Total*
G1	1			1
G2		1		1
G3		2		2
In situ				0
Total	1	3	0	4

At present FMC studies are performed using bladder washouts obtained during cystoscopy. This limits the use of the technique for diagnosis of new cases. Four grade 1 non-invasive tumours could have been diagnosed by FCM alone and two were suspicious, with 10 to 15% of cycling hyperdiploid cells. Ten of the grade 1 tumours had an increased RNA before treatment and this finding corresponds with that in other studies (Melamed, 1984). A comparison needs to be made between bladder washout FCM and voided urine FCM because if similar accuracy could be obtained the technique would have a wide application as a non-invasive method of bladder tumour follow-up. We chose bladder washout samples because they contain a much higher bladder mucosal cells content than voided urine samples.

The most interesting finding was an increase in

RNA during treatment in the patients who later developed recurrence. This change was detected before any other indication of recurrence. The reason for this increase is not yet known, but if this finding is confirmed in a larger series it may indicate patients who will not respond to intravesical treatment and in whom more aggressive treatment would be warranted.

Flow cytometry is a sophisticated technique requiring expensive apparatus and considerable technical expertise. Nevertheless, the technique has a wide variety of applications and is likely to become more widely available. Because large numbers of cells are measured, the objectivity of the technique is good when compared with other techniques of tumour assessment. We have shown that increased RNA content of cells may predict patients liable to suffer tumour recurrence. Furthermore, this change may be one of the earliest that can be detected. There is a need for investigation of a larger series and for evaluation of flow cytometry during other methods of bladder tumour treatment. If our preliminary findings are confirmed, flow cytometry could become an important tool in the management of bladder cancer.

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The Authors

G. G. Hadjissotiriou, MD, PhD, Honorary Urological Registrar.
D. K. Green, BSc, PhD, Senior Scientist.
M. A. McIntyre, MRCPath, Consultant Pathologist.
T. B. Hargreave, MS, FRCS, Senior Lecturer, Honorary Consultant Urological Surgeon.
G. D. Chisholm, ChM, FRCS, Professor of Surgery, Honorary Consultant Urological Surgeon.

Requests for reprints to: T. B. Hargreave, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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The Influence of Retinoic Acid Receptor (RAR) Status of Bladder Tumours on the Course of the Disease

A. R. de BOLLA, R. M. SHAVE, S. L. FAGG, K. HEALD, M. A. HUGHES, D. M. A. WALLACE and P. DAWSON EDWARDS

Departments of Urology and Medicine, Queen Elizabeth Hospital, Birmingham

Summary—Retinoids influence bladder tumour development in animals and tumour recurrence in man. Some human tumours contain intracellular receptor proteins for retinoids. The effect of the presence of such retinoic acid receptors (RAR) on tumour response to conventional therapy has been studied in 59 patients. Thirty-two of 36 RAR + ve and 11 of 23 RAR − ve tumour patients were alive after a mean follow-up period of 2.6 years. Higher stage and grade were more commonly associated with RAR − ve tumours. Independent of stage, recurrence was more common in RAR − ve tumours. These studies suggest that RAR − ve tumours are more likely to recur and more likely to become invasive. However, further studies are required to determine the clinical value of RAR receptor status as a prognostic indicator.

The retinoid group of substances includes vitamin A (or trans retinol) and its naturally occurring oxidation products trans retinal and trans retinoic acid, and a number of synthetic analogues. Retinoids have been known to be potent agents for the control of cellular differentiation and proliferation for more than 50 years (Wolbach and Howe, 1925), but more recently their ability to influence carcinogenesis in experimental animals has been appreciated (Bollag, 1979). *In vitro* experiments in which retinoids have shown an ability to suppress the proliferation of certain fully transformed neoplastic cells (Lotan, 1980) have increased the interest in this group of compounds.

Dietary deficiency of vitamin A in animals leads to metaplastic changes in the epithelial linings of the respiratory, alimentary and urogenital tracts. The similarities between these and certain premalignant states led to the concept that cancers might be prevented by the administration of vitamin A or other retinoids of lower toxicity (Bollag, 1979). Studies in humans have related an increased risk of lung cancer to low serum vitamin A levels (Wald *et al.*, 1980) and an increased risk of bladder cancer to low dietary intake (Mettlin and Graham, 1979). Bladder epithelium is known to depend on retinoids for the maintenance of normal cellular differentiation. Sporn *et al.* (1977) showed that the development of chemically induced tumours in rat bladders could be inhibited by feeding the animals 13 cis retinoic acid, and Alfthan *et al.* (1983) showed a reduction in the recurrence rate of superficial papillary tumours following the administration of retinoids to patients.

The actions of retinoids are thought to be mediated by specific intracellular binding proteins with which they form complexes. Retinoic acid receptors have been demonstrated in some human bladder tumours (Fagg *et al.*, 1982) but it is not known whether the presence or absence of RAR reflects differences in the nature of tumours or affects their response to conventional forms of antitumour therapy. We have therefore reviewed the clinical course of 59 patients in whom bladder tumour specimens were assayed for the presence of RAR.

Patients and Methods

Specimens of transitional cell bladder tumours were obtained by transurethral resection from 59

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patients between 1980 and 1983. These specimens were then processed to determine the presence of RAR in the tissue. Thirty-nine of these tumours came from newly diagnosed patients and 20 from patients attending for follow-up. There were 48 males (mean age 68 years) and 11 females (mean age 66 years). Of those previously treated, all had undergone cystodiathermy, whilst six had also received radiotherapy, four systemic chemotherapy and one intravesical chemotherapy. Patients were followed up at 3- to 6-monthly intervals and their treatment was decided in accordance with the usual practice of the surgeons concerned, the RAR status of the tumour being disregarded. The clinical course of the patients has been reviewed retrospectively from the time of tumour biopsy and RAR assay. Tumours were classified according to the TNM systems of the UICC (1978) and graded according to the WHO classification (Mostofi *et al.*, 1973).

Tumour specimens were removed from the operating theatre on ice and assayed for RAR as described in detail previously (Fagg *et al.*, 1982). The tissue was cooled to −40°C, pulverised, resuspended and centrifuged. The resulting cytosol was then incubated overnight with tritium-labelled all trans 11, 12, 3H-retinoic acid. Excess free retinoic acid was removed using charcoal and 50 µl of the treated cytosol were then analysed by agarose gel electrophoresis. The electrophoretic strips were divided into segments and the gel eluted overnight. Tritium counting was then performed using a scintillation counter. Patients whose tumours had detectable levels of RAR were designated RAR positive (RAR + ve), the remainder being deemed RAR negative (RAR − ve).

Results

No RAR was detected in tumours from 23 patients. In 36 patients (28 males and 8 females), RAR was detected in concentrations varying between 0.11 and 77.3 pmol/mg cytosol protein, with a mean of 4.36 pmol/mg. The distribution of tumour stages and grades within the RAR + ve and RAR − ve groups is shown in Table. 1. Only 7 RAR + ve tumours (19%) were invading muscle, whereas 11 RAR − ve tumours (48%) did so ($P = 0.05$ χ^2 5.33). A greater proportion of the higher stage, higher grade tumours fell into the RAR − ve group.

Patients were followed up until their death. Table 2 details the mortality, rate of recurrence and incidence of disease progression in the RAR + ve and RAR − ve groups. Survival amongst RAR + ve patients was 89% compared with 48% for RAR − ve patients ($P = 0.001$ χ^2 11.97). Nearly one-third of RAR + ve patients were free from recurrence during follow-up as opposed to only two RAR − ve cases (9%). When compared by T category, 11 (38%) pTa and pT1 RAR + ve tumours were recurrence-free, but only 2 (17%) RAR − ve superficial tumours had no recurrence. Similarly, 2 of 3 patients with RAR + ve pT3 tumours survived the period of follow-up but only 1 of 6 RAR − ve patients did so. All tumours were treated endoscopically. In addition, some patients had one or more other forms of treatment as shown in Table 3. The

Table 1 Tumour Stage and Grade

Tumour grade and category	*RAR + ve* *Number*	 *Mean conc. pmol/mg*	*RAR − ve* *Number*
pTA	12	1.99	8
pT1	17	7.2	4
T2	3	0.67	3
T3	3	2.27	6
T4	1	1.94	2
G1	16	1.77	7
G2	17	7.18	10
G3	3	2.2	6

Table 2 Mortality, Recurrence Rate and Progression of Disease

	RAR + ve	*RAR − ve*
Alive	32 (89%)	11 (48%)
Mean follow-up	2.5 yrs	2.75 yrs
Dead	4 (11%)	12 (52%)
No recurrence	11 (31%)	2 (9%)
Recurrence once	7	1
Recurrence > once	18	20
Progression		
T category	7 (19%)	7 (30%)
Grade	5 (14%)	3 (13%)

Table 3 Details of Treatment

Treatment	*RAR + ve*	*RAR − ve*
Radiotherapy	8 (22%)	12 (52%)
Systemic chemotherapy	4 (11%)	3 (13%)
Intravesical chemotherapy	3 (8%)	1
Cystectomy	3 (8%)	1

higher use of radiotherapy in RAR − ve tumours reflects the higher proportion with muscle invasion.

Discussion

The possibility that human bladder tumours might be prevented by the administration of retinoids is an exciting concept, encouraged by the apparent control of neoplastic cell development in cell culture studies (Lotan, 1980). However, the relatively low therapeutic index and high toxicity of the currently available retinoids limits their clinical use, though early studies have shown promising results (Alfthan *et al.*, 1983; Studer *et al.*, 1984). The mode of action by which retinoids control cell growth and differentiation is still debated (Bollag, 1979; Sporn and Roberts, 1983) but it seems likely that they act like hormones, forming complexes with intracellular receptor molecules. These complexes then bring about some modification of gene transcription. Receptors to retinoids have been detected in human breast and lung tumours (Ong *et al.*, 1975) as well as bladder tumours. These workers did not find receptors in the surrounding normal breast and lung tissue, but Kung *et al.* (1980) did detect low concentrations of retinoid receptors in normal breast tissue. Similar receptors have been found in experimentally induced animal tumours (Sani and Corbett, 1977). It appears that normal tissues have absent or low levels of receptors, while they are increased in pre-neoplastic and neoplastic tissues (Bollag, 1979).

It would seem that the presence of RAR, or at least higher levels of them, might reflect a departure from the normal state of healthy urothelium. The quantity of tissue required for our assay precluded investigating normal human transitional cell epithelium for the presence of RAR. Since none of our patients was treated with retinoids, their clinical course reflects the inherent nature of the tumours and their response to conventional therapy. From the above it might have been expected that RAR + ve tumours would have more neoplastic characteristics than RAR − ve tumours. Our results show that this was not the case. A significantly higher survival rate was seen in RAR + ve tumours (89% *vs* 48%) and, stage for stage, a lower rate of tumour recurrence was seen in the RAR + ve group. The presence and concentration of RAR was not dependent on tumour category or grade, though higher stage and grade tumours were more likely to be RAR − ve in this study. Further work in this field will require a more sensitive assay so that low levels of RAR can be accurately determined in small tissue samples, as are available from cold cup biopsies of non-tumour bearing urothelium.

Neoplastic transformation may be initially associated with the appearance of RAR, but the ability of the cells to form receptors may be lost as dedifferentiation progresses. This may be analogous to the loss of ABO antigens seen in bladder tumours (Decenzo *et al.*, 1975). The rate of metabolic change occurring within cells during dedifferentiation may be different from the more widely recognised histological changes. This could account for some apparently low stage, low grade tumours being RAR − ve and having an increased potential for recurrence and invasion.

It remains to be established whether the presence or absence of retinoid receptors in human bladder tumours will be a useful prognostic indicator. More knowledge is needed of the receptor status of normal and infected human urothelium and in carcinoma *in situ*. It is likely that areas within larger tumours may differ in their receptor status and this may cause sampling errors. The findings of this study suggest that RAR − ve tumours may be more likely to recur and more likely to become invasive. If these findings are substantiated, this may have implications for the treatment of superficial RAR − ve tumours. The response of superficial bladder tumours to treatment with synthetic retinoids should be studied prospectively according to the RAR status of the tumour and the non-tumour bearing urothelium.

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The Authors

A. R. de Bolla, FRCS, Senior Urological Registrar.
R. M. Shave, MB,BS, Surgical Registrar.
S. L. Fagg, FRCS, Senior Urological Registrar.
K. Heald, BSc, Scientific Officer.
M. A. Hughes, FRCS, Consultant Urologist.
D. M. A. Wallace, FRCS, Consultant Urologist.
P. Dawson Edwards, FRCS, Consultant Urologist.

Requests for reprints to: A. R. de Bolla, Department of Urology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

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The Effect of Intravesical Thiotepa on the Recurrence Rate of Newly Diagnosed Superficial Bladder Cancer

An MRC Study

* MRC WORKING PARTY ON UROLOGICAL CANCER, LONDON

Summary—Four hundred and seventeen patients with newly diagnosed superficial bladder tumours (Ta or T1) were treated with complete transurethral resection and then randomised between three groups. Group 1 had an instillation of 30 mg thiotepa at the time of primary treatment. Group 2 had instillations of thiotepa at 3-monthly intervals for a year. Group 3 was given no instillation. Regular check cystoscopies revealed no significant difference in the rate at which tumours recurred in the three groups ($p = 0.4$ and $P = 0.7$ for control *vs* thiotepa given once and five times respectively). It was concluded that neither thiotepa regimen produced sufficient improvement to justify its use in this group of patients.

Though intravesical instillation of thiotepa after TUR reduces the number of recurrences of superficial bladder cancer (Burnand *et al.*, 1976; Soloway, 1980; England *et al.*, 1981; Koontz *et al.*, 1981; Fosså *et al.*, 1983; Green *et al.*, 1984), it is not clear how frequently instillations have to be given to produce this beneficial effect. Most regimens employ repeated instillations, often continuing for months. Attending for an instillation is a nuisance for the patient, as well as being costly for both patient and hospital, and the study reported here was undertaken to see whether a very simple regimen—instillation of intravesical thiotepa at the time of primary resection of newly diagnosed superficial bladder cancer—is effective in reducing the recurrence rate.

Patients and Methods

Between December 1981 and February 1984, 417 patients with newly diagnosed Ta or T1 transitional cell carcinoma of the bladder from 15 institutions (Table 1) were entered into the study. They were required to be free of urinary tract infection, to have an adequate performance status (0-2 WHO), and a WBC above 3×10^9/l and platelets above 100×10^9/l. After complete transurethral resection, tissue was sent to the referee pathologist from the tumour itself and from normal urothelium at two sites, one near to the tumour and one remote from it. The patients were then randomly allocated to one of three groups:

Group 1 (thiotepa × 1) received a single instillation of 30 mg thiotepa in 50 ml saline immediately following transurethral destruction of the tumour. No further instillation was given to patients in this group.

Group 2 (thiotepa × 5) received in addition further instillations of 30 mg thiotepa at 3-monthly check cystoscopies for 1 year (5 instillations in all).

Group 3 (control) had no instillations.

Check cystoscopy was planned 3-monthly for a year, at least 6-monthly for a further 2 years and annually thereafter. At each visit a check was made for any side effects attributable to the treatment.

Of the 147 patients, 38 were ineligible for the reasons listed in Table 2, most commonly because unexpected muscle invasion was found on histological examination. Excluding 38 patients leaves 379 patients for analysis.

Patient characteristics are listed in Table 3. There were minor differences between groups in the

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

* The participants in the study are listed in Table 1.

Table 1 Participants

Centre	*Investigator*	*Number*
Airedale	I. Appleyard W. A. F. McAdam	28
Castleford	M. R. G. Robinson	14
Derby	K. Munson	36
Edinburgh, Royal Infirmary	D. Tolley	17
Edinburgh, Western General	G. D. Chisholm T. Hargreave J. Newsam	36
Hull	D. W. W. Newling	41
Leeds	P. H. Smith P. Whelan R. E. Williams	35
London Hospital	J. P. Blandy H. England A. Paris	9
Newcastle	R. R. Hall P. Ramsden	37
Newport	W. B. Peeling	15
Oxford	G. Fellows J. C. Smith	22
Sheffield	J. L. Williams	50
Swansea	M. B. Rose K. Vaughton	26
Wakefield	R. S. Adib	34
York	B. Richards	17

Table 2 Ineligible Patients

Number of patients		417
Eligible		379
Ineligible:		38
Inappropriate histology	28	
No follow-up	9	
Surgeon other than consultant or SR	1	
Total	38	

distribution of these characteristics: for example patients with tumour diameter greater than 5 cm were less common in the thiotepa × 5 group, while G3 tumours were less common in the control group. These differences were allowed for in analysis and do not affect the conclusions.

Results

Of the 379 eligible patients, 12 had not contributed follow-up information because:

(i) Three (control) patients died of unrelated causes before the first cystoscopy was due.
(ii) Four (two control, 1 thiotepa × 1, 1 thiotepa × 5) refused to attend.
(iii) Two (control) patients went off study as a result of a local pathologist's report.
(iv) Three (1 thiotepa × 1, 2 thiotepa × 5) had a recurrence at the first check cystoscopy which was not biopsied, and developed no subsequent recurrence. It was not possible to tell with confidence whether these patients had developed a recurrence or not.

Toxicity

One patient developed fluid retention and oedema after each instillation of thiotepa. On the third occasion this was severe and the patient declined further instillation. Three further patients receiving thiotepa developed urinary frequency and scalding and in one of these a rash was noted.

Recurrence Rate

Of 367 patients with follow-up information, 143 have developed at least one recurrence (Table 4). Recurrence-free rates calculated by the life-table method (Peto *et al.*, 1977) are shown in the Figure, which indicates that approximately 45% of patients will have developed a recurrence within 2 years of the initial TUR. The proportion of patients free of recurrence appears slightly greater in the control group. The difference between the curves is not statistically significant—the results of the Logrank tests comparing them are shown in Table 4. The recurrence-free rate takes account of only the first recurrence after initial treatment. To look at the frequency of recurrences a "positive cystoscopy rate" may be calculated as the number of cystoscopies at which a recurrence would be seen in 100 patient months of follow-up. The data are presented in Table 5. It can be seen that the estimated positive cystoscopy rate is somewhat lower in the control group than in either of the thiotepa groups. There is also a tendency for the number of positive cystoscopies to decrease over the 12-month period.

The recurrence rate can alternatively be expressed by counting the number of recurrent tumours per 100 patient months (Table 6). It can be seen that the thiotepa × 5 group appeared to have a larger average number of tumours than either of the other two groups, although the figures were strongly influenced by the few patients with large numbers of recurrent tumours. The results shown in Tables 5 and 6 have not been submitted to statis-

Table 3 Patient and Disease Characteristics at Entry to Trial

		Control (*n* = *130*)	*Thiotepa* × *1* (*n* = *126*)	*Thiotepa* × *5* (*n* = *123*)	*Total* (*n* = *379*)	%
Age (years)	19-50	21	17	17	55	14
	51-59	34	22	30	86	23
	60-69	40	54	45	139	37
	70-79	31	31	28	90	24
	80-89	4	2	3	9	2
History of symptoms (months)	0-3	68	79	74	221	58
	4-11	33	26	28	87	23
	12+	29	21	21	71	19
Maximum tumour diameter (cm)	Up to 2.5	76	80	77	233	62
	2.6-4.9	33	29	35	96	25
	5.0+	21	18	11	50	13
Number of tumours	1	90	88	89	267	71
	2	24	22	20	6	17
	3+	16	16	14	46	12
Tumour category	pTa	102	91	93	286	76
	pT1	18	23	19	60	16
	pTx	9	12	11	32	8
	Not known	1	0	0	1	—
Tumour grade	G1	80	82	69	231	61
	G2	39	29	38	106	28
	G3	9	14	16	39	10
	GX	1	1	0	2	1
	Not known	1	0	0	1	—

Table 4 Comparison of Recurrence-Free Rates in the 3 Treatment Groups by Logrank Test

	Treatment			
	Control	*Thiotepa* × *1*	*Thiotepa* × *5*	*Total*
Number patients eligible	130	126	123	379
Number patients with follow-up information	123	124	120	367
Observed number patients with a recurrence	46	52	45	143
Logrank test				
Expected number patients with a recurrence	49.6	47.8	45.6	143.0
Control v Thiotepa × 1				
χ^2 (*P*-level)		0.7 (0.4)	—	
Recurrence-risk ratio (95% confidence limits)		1.19 (0.79, 1.79)	—	
Control v Thiotepa × 5				
χ^2 (*P*-level)			0.1 (0.7)	
Recurrence risk ratio (95% confidence limits)		—	1.08 (0.70, 1.64)	

tical tests, but it is clear that the thiotepa groups did not have more favourable rates than the control group.

The figures given so far are for recurrences proved by biopsy. In a proportion of cases a biopsy was omitted. Analysis of the results taking into account clinical evidence of recurrence only yields figures which are essentially similar.

Table 7 shows the factors found to relate to prognosis in this study. Some of the influential factors (*e.g.* tumour grade) were not evenly balanced between the treatment groups (Table 3). A Cox regression analysis (Cox, 1972) was performed to examine differences between the recurrence-free rates of the treatments adjusting for imbalances in maximum tumour diameter, number of tumours, tumour category and tumour grade. This analysis confirmed that these imbalances had no material impact on the logrank test results reported earlier in this section.

Progression

Nine patients in the study developed tumours invading muscle, two having control treatment,

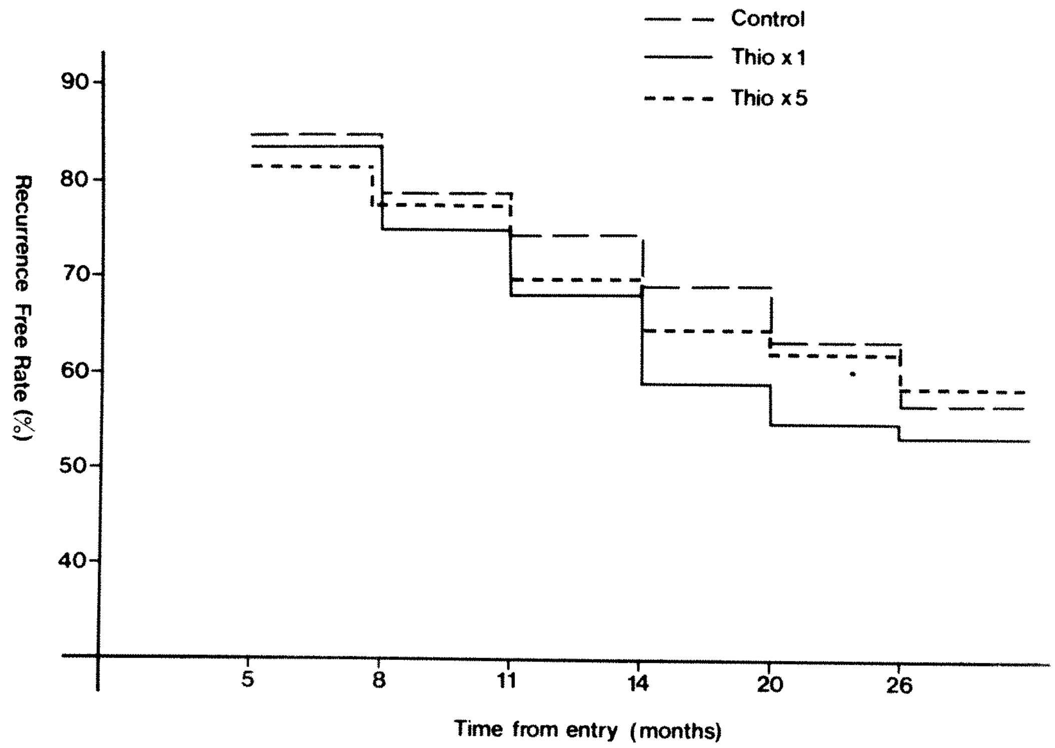

Fig. Recurrence-free rates in the three treatment groups.

Table 5 Positive cystoscopy Rates Over First 12 Months of Follow-up

	Treatment		
	Control	*Thiotepa × 1*	*Thiotepa × 5*
Number of patients with follow-up information	123	124	120
Number of positive cystoscopies			
0-3 months	17	20	21
3-6 months	18	16	12
6-9 months	12	14	15
9-12 months	8	15	15
0-12 months	55	65	63
Positive cystoscopies per 100 patient-months	3.8	4.6	4.6

three thiotepa × 1 and four thiotepa × 5. Seven of these nine patients had a pT1 tumour at initial presentation, and eight of nine had grade three tumours.

The significance of histological change in "normal" urothelium is proving difficult to evaluate, but will be the subject of a separate report.

Discussion

The main result is that instillation of 30 mg thiotepa at the time of tumour resection does not improve the recurrence rate. This holds good whether the recurrence rate is measured by counting the proportion of patients free of recurrence at various times, the number of cystoscopies at which recurrence is noted, or the total number of individual recurrences found per year.

Regimens for intravesical chemotherapy vary widely from instillation at the time of check cystoscopy only (Burnand *et al.*, 1976; Abrams *et al.*, 1981; Kurth *et al.*, 1983) to instillation 3 times a week (Mishina *et al.*, 1975). The optimal duration and frequency of a treatment course has yet to be

Table 6 Recurrent Tumour Rates in the First 12 Months of Follow-up

	Treatment		
	Control	*Thiotepa × 1*	*Thiotepa × 5*
Number of patients with follow-up information	123	124	120
Number of recurrent tumours			
0-3 months	38	27	46
3-6 months	51	29	31
6-9 months	42	31	69
9-12 months	28	37	78
0-12 months	159	124	224
Number of recurrent tumours per 100 patient-months	11.1	8.8	16.3

Table 7 Prognostic Factors

		Number patients	*Recurrence-free rate*	
			12 m	*24 m*
Size of tumour	< 2.5 cm	226	76%	69%
	2.6-4.9 cm	94	61%	44%
	5.0 + cm	47	57%	34%
No. tumours	1	258	77%	65%
	2	64	57%	47%
	3 +	45	47%	32%
Stage	pTa	276	73%	61%
	pT1	58	50%	39%
	pTx	32	75%	66%
Grade	G1	224	75%	64%
	G2	102	70%	57%
	G3	38	34%	23%

established (Bouffioux, 1985). Clearly a simple regimen would be preferable to a complex one of similar effectiveness.

Several reports have suggested that a simple regimen such as that employed in the present study effectively reduces the recurrence rate. For example, Burnand *et al.* (1976) treated 19 patients with a single instillation of thiotepa immediately after TUR and found a substantial reduction in the number developing further tumours compared with 32 patients in the control group. Unfortunately, this trial was less convincing than it might have been because the numbers were small, the disparity in numbers between the treated and control arms raised some doubt about the randomisation mechanism, and the rate of recurrence in the control arm (31 of 32 patients) was surprisingly high. These results have not been confirmed in the present study, perhaps because it was limited to newly diagnosed patients or because it was much larger.

The clinical value of an improvement in recurrence rate following addition of intravesical chemotherapy to routine TUR depends on whether it is sufficient to make up for any disadvantages attributable to the new treatment (Richards, 1984).

Counting the cost of treatment is a difficult exercise, requiring an assessment of inconvenience and toxicity as well as expense before it is possible to decide whether a change in clinical progress means that the new treatment is actually better for the patient (Freedman and Spiegelhalter, 1983). At the beginning of the study participants agreed that an improvement of 5 to 10% in the 2-year recurrence rate would be necessary to justify the regimen of one instillation, and that an improvement of 10 to 15% would be required to justify five instillations. The 95% confidence limits for the improvement in recurrence-free rates are −21 to +7% for the thiotepa × 1 and −20 to +8% for thiotepa × 5. It is concluded that neither regimen produces sufficient improvement to justify its use in this group of patients.

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The Authors

The MRC requires reports to be attributed to the MRC and not to individual authors. Participants and their institutions are listed in Table 1.

Requests for reprints to: B. Richards, Department of Urology, York District Hospital, Wigginton Road, York YO3 7HE.

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Mitomycin C in Superficial Bladder Cancer: 24-month Follow-up

J. J. F. SOMERVILLE, D. W. W. NEWLING, B. RICHARDS, M. R. G. ROBINSON and P. H. SMITH

Departments of Urology, St James's University Hospital, Leeds; Princess Royal Infirmary, Hull; York District Hospital and Pontefract General Infirmary

Summary—Twenty-three patients who were given intravesical Mitomycin C for treatment of superficial bladder cancer have been followed up for a further 12 and 24 months after an initial assessment 5 weeks after completing therapy. At 5 weeks 17 (74%) showed complete disappearance of tumour and 4 (17%) showed a partial response. Twelve months later 8 (35%) remained tumour-free and 15 (65%) had recurrences; 5 of these (22% of all patients) had progressed to invasive cancer. The results at 24 months were little different except that one further patient (27% in all) progressed to invasive cancer.

Six patients with symptomatic carcinoma *in situ* became symptom-free after Mitomycin C, but despite remaining free of symptoms three have progressed to invasive cancer.

This small series shows that involvement of large areas of bladder urothelium by tumour, carcinoma *in situ* and previous therapy for tumour are unfavourable prognostic indices.

The use of intravesical chemotherapy either for treatment of superficial bladder cancer or for prophylaxis after transurethral resection is becoming more widespread. In this regard the alkylating agent Mitomycin C has been gaining in popularity in recent years, after favourable reports from Mishina *et al.* (1975), Mishina and Watanabe (1979), Soloway (1980), Soloway *et al.* (1981) and Prout *et al.* (1982). The review of the Japanese experience with intravesical Mitomycin C has shown it to be both highly effective in the treatment of superficial bladder cancer and to be free of serious side effects (Mishina and Watanabe, 1979). The Yorkshire Urological Cancer Research Group, anxious to undertake a study with Mitomycin C to establish the optimum frequency, dosage and duration of treatment, carried out a Phase II study using the treatment regimen adopted by Mishina *et al.* (1975). The results confirmed that toxic side effects from the intravesical use of Mitomycin C were acceptably low and no life-threatening side effects were seen in any of the patients. It further demonstrated that Mitomycin C had a highly potent antitumour effect in that 95% of the 23 patients entered showed either a complete or partial response to the treatment (Harrison *et al.*, 1983).

We felt it important to examine the further course of these patients in the light of their excellent initial response and all have been followed up for at least 2 years. This report presents the follow-up results at 12 and 24 months after completing treatment.

Patients and Methods

Twenty-three patients with biopsy-proven superficial bladder cancer were entered into the Phase II study. No tumours were resected but additional biopsies were also taken of cystoscopically normal and abnormal bladder mucosa to detect possible *in situ* change. It was intended that patients entered should have become difficult to manage endoscopically, either because of the frequent appearance of

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Presented at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985 recurrent tumours or multiple tumours, or because of the presence of associated areas of carcinoma *in situ*, but this was not always the case. Twenty-one instillations of 20 mg Mitomycin C in 20 ml water were given over a 7-week period, according to the recommendations of Mishina *et al.* (1975), and cystoscopy was carried out at 4, 8 and 12 weeks after starting treatment. No tumours were resected until 12 weeks, when the response to treatment was assessed by further biopsies of suspicious and normal-looking bladder mucosa. Urine cytology was not routinely used in assessment.

Further information is shown in Tables 1 and 2; further details of the Phase II study have been reported elsewhere (Harrison *et al*, 1983).

Table 1 Bladder Involvement (23 patients)

Minimal	6 (26%)
<25%	8 (35%)
25-50%	7 (30%)
>50%	2 (9%)

Table 2 Details of Patients

Histological grade + T category			
Grade I	7 (30%)	Ta	3 (1 with 2° TIS) (13%)
Grade II	13 (57%)	T1	17 (2 with 2° TIS) (74%)
Grade III	1 (4%)	1° TIS	3 (13%)
Not stated	2 (9%)		
	23		23

Previous treatment (16 patients)	
Mean period	36.4 months (range 3 mths-9 yrs)
Endoscopy alone	9
Pyridoxine	3
BCG	2
Chemotherapy	2

Six patients were entered into the study at the time their bladder tumours were first diagnosed. The notes of one patient cannot be traced.

Results

The results of the study have been assessed at three periods—at 5 weeks after treatment (the end of the Phase II study), and at 12 and 24 months after completing treatment.

1. *Overall Results*

a. *Results at 5 weeks* (Phase II study)

The detailed results of the initial study were reported by Harrison *et al.* (1983) but for the purpose of discussion the pertinent facts are summarised. Of the 23 patients, 17 (77%) demonstrated complete disappearance of all tumour, while a further four (18%) showed a partial response. One patient failed to respond and another was withdrawn after nine treatments because of the development of a skin rash after each instillation. A particularly gratifying response was seen in the six patients with carcinoma *in situ*, all of whom had marked irritative bladder symptoms before treatment; all six became symptom-free after the Mitomycin C therapy and there was complete disappearance of disease in five. The remaining patient showed a partial response.

Toxicity to Mitomycin C was observed in six patients and consisted of urinary infection (2 patients), chemical cystitis (2), skin rash (3) and thrombocytopenia (1). Some patients demonstrated more than one side effect. In five patients treatment was terminated because of toxicity after 9, 13,18, 18, and 18 instillations respectively instead of the scheduled 21.

b. *Results at 12 months* (23 patients)

Twenty-two patients (96%) were alive. One had died of invasive bladder cancer 11 months after completing treatment. Eight (35%) remained free of recurrence, 10 (43%) had recurrence controlled endoscopically, but 5 (22%) had progressed to invasive cancer at a mean interval of 6.4 months (range 2–12 months) after completing treatment.

c. *Results at 24 months* (22 patients)

The hospital notes for one patient cannot be traced, but assessment in this patient up to 13 months had already been noted. The results relate to the remaining 22 patients.

Eighteen patients (82%) were still alive and four (18%) had died—three of invasive bladder cancer and one of carcinoma of the caecum. Seven patients (32%) were free of recurrent tumour, 9 (41%) had endoscopically controlled tumour and 6 (27%) had progressed to invasive cancer. The results at 24 months were little changed from those at 12 months, except that two patients who were alive with invasive disease at 12 months had died by 24 months, and one additional patient had developed invasive disease. These results are summarised in Table 3.

Table 3 Results of Follow-up

	5 weeks	*12 months*	*24 months**
Tumour-free	17 (74%)	8 (35%)	7 (32%)
Recurrence	6 (26%)	10 (43%)	9 (41%)
Invasion (dead)	0 (0%)	5 (1) (22%)**	6 (4) (27%)

* One patient's notes cannot be traced.

** One patient had T2 tumour 16 months prior to entry, although this was not confirmed by biopsy in the Phase II study.

2. *Complete Responders*

Of particular interest is the subsequent course of those patients who demonstrated a complete response in the Phase II study. Of the 17 patients only seven remained recurrence-free at 24 months; five had progressed to invasive bladder cancer, and three of these died from the disease. The remaining five have superficial recurrences controlled endoscopically.

3. *Carcinoma in situ*

There were six patients in this group—three with primary and three with secondary carcinoma *in situ*, all of whom complained of marked irritative bladder symptoms before treatment. After Mitomycin C therapy all were rendered symptom-free and remained so throughout follow-up. Nevertheless, three of these patients have progressed to invasive bladder cancer at a mean interval of 6.3 months (two have died of the disease, both at 15 months after completing treatment). Of the other three patients, two remained recurrence-free and one has recurrences managed endoscopically.

The particularly worrying feature about this group was that the relief of symptoms induced in these patients by the Mitomycin C was maintained even in those patients whose tumours subsequently became invasive.

4. *Invasive change*

Six patients progressed to invasive bladder cancer at a mean interval of 8.2 months (range 2-16 months). In the Phase II study five showed complete disappearance of all tumour and one failed to show any response at all after Mitomycin C. Histology in this group was: primary carcinoma *in situ* (2 patients), secondary carcinoma *in situ* with G2T1 tumour (1), G1Ta (1), G1T1 (1), G2T1 (1). The mean time to first recurrence was 6.5 months (range 2-13 months) compared with 5.7 months for those with superficial recurrences (range 0-26 months). There was no significant difference in the time the patients had received prior treatment for their bladder cancer in those remaining free of recurrence (28.1 months), those with superficial recurrences (24.4 months) and those with infiltrating recurrences (27.5 months).

Three patients have died of the disease at a mean interval of 13.7 months after completing treatment (range 11-15 months). Apart from carcinoma *in situ*, the other unfavourable prognostic factors were previous treatment with pyridoxine or intravesical chemotherapy and the extent of bladder involvement, with the greater the area of tumour involvement the higher the chance of progression to invasive disease (Table 4).

Table 4 Results at 24 Months Related to Tumour Extent

	Degree of bladder involvement	
	<25% (14 patients)	*>25% (9 patients)*
Tumour-free	5 (36%)	2 (22%)
Recurrences	6 (43%)	4 (44%)
Invasion	3 (21%)	3 (33%)

The grade of the tumour did not influence the subsequent course in this series.

Close scrutiny of the notes of all patients revealed that one patient had been found to have very early tumour involvement of bladder muscle 16 months before entry into the study, although this was not confirmed at either the initial biopsy or the biopsy on completion of the Phase II study. Invasive change was ultimately diagnosed in this patient 12 months after completion of the Phase II study and he died 3 months later.

Discussion

Despite the excellent short-term results (Harrison *et al.*, 1983), the findings at 12 and 24 months in this small series are disappointing, with six patients progressing to invasive cancer at a mean interval of 8.2 months after completing treatment. The results at 24 months differ little from those at 12 months. Only 1 of 8 patients who were recurrence-free at 12 months demonstrated recurrences at 24 months, and only 1 of 10 patients with recurrences at 12 months progressed to invasive disease. These results suggest that the critical time for evaluating the response to Mitomycin C treatment lies between 5 weeks and 12 months after completion of therapy. It may also be relevant that in 5 of the 6 patients developing invasive disease, progression was noted at the time of first assessment.

It is difficult to know why this small group of patients should have done so badly and comparison with other studies is unhelpful because so many variables can exist. From the Japanese experience (Mishina *et al.*, 1975), these tumours should have responded favourably, as the individual tumours were all of small size, low stage and low grade. It has been suggested in another series that treatment failure relates more to low dosage of Mitomycin C (less than 25 mg Mitomycin C per instillation) than to tumour extent (Bracken, 1982); if so, this should have been evident at the 5-week assessment.

Although many of the patients in this study were high risk, not all were. Six (26%) had received no prior treatment for bladder cancer and were entered at the time of first diagnosis, and an additional six (26%) had bladder involvement described as "minimal". Fourteen of the 23 patients (61%) had less than 25% of their bladder involved with tumour.

In contrast to the findings of other workers, that small papillary tumours respond well to Mitomycin C regardless of numbers (Soloway *et al.*, 1981; Bracken, 1982, Mishina *et al.*, 1982; Prout *et al.*, 1982), extensive bladder involvement with such tumours was an unfavourable prognostic index in this series when the results were reviewed at 12 months, although at 5 weeks the response had been excellent.

This small series has shown that an assessment made in the short term after treatment with Mitomycin C may not be a reliable index of subsequent behaviour and that the true nature of the response is more likely to be seen 12 months after treatment.

A particularly watchful eye must be kept on patients with *in situ* carcinoma, in whom the asymptomatic progression to invasive disease is a particularly worrying feature.

Mitomycin C did not appear to halt the invasive character of a tumour and unfavourable prognostic signs were the presence of carcinoma *in situ* and extensive involvement of bladder urothelium with tumour.

It is hoped that the current EORTC and MRC studies with Mitomycin C will shed more light on the place of this drug in the treatment and prophylaxis of superficial bladder cancer. In the meantime, we advocate caution in interpreting the results of intravesical chemotherapy in high risk patients based on assessments made only in the short term.

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The Authors

J. J. F. Somerville, MA, MD, FRCSE, formerly Senior Urological Registrar, Leeds and Bradford. Now Consultant Surgeon in Urology, Halifax General Hospital.

D. W. W. Newling, FRCS, Consultant Urologist, Princess Royal Infirmary, Hull.

B. Richards, MD, FRCS, Consultant Urologist, York District Hospital.

M. R. G. Robinson, FRCS, Consultant Urologist, Pontefract General Infirmary.

P. H. Smith, FRCS, Consultant Urologist, St James's University Hospital, Leeds.

Requests for reprints to: J. J. F. Somerville, Department of Urology, Halifax General Hospital, Salterhebble, Halifax HX3 OPW.

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First-line Intravenous Cisplatin for Deeply Invasive Bladder Cancer: Update on 70 Cases

B. S. PEARSON and D. RAGHAVAN

For members of the Urological Cancer Research Unit, Royal Prince Alfred Hospital, Sydney, and Illawarra Urology Unit, Wollongong, Australia*

Summary—Seventy patients with T2-T4 NX MO bladder cancer were treated with intravenous cisplatin (100 mg/m^2 *q* 3-weekly) followed by radiotherapy and/or cystectomy. Objective responses to cisplatin were seen in 57%. For the first group of 50 patients (treated between August 1981 and November 1983), the actuarial survival rate at 2 years was 64%, with a median survival of 20+ months: 81% of deaths occurred within 18 months of entry. Most relapses occurred in the bladder/pelvis. A randomised, controlled study is in progress to assess the true value of this approach to the treatment of invasive bladder cancer.

The established treatments of invasive bladder cancer, including cystectomy, radiotherapy, or a combination of both, have each yielded 5-year survival rates of less than 40 to 50% (Skinner, 1980; Bloom *et al.*, 1982; Raghavan, 1985). Most of the evidence from clinical and autopsy studies suggests that micrometastases are usually present at the time of the first presentation (Skinner, 1980). Relapses usually occur within 12 to 18 months of initial treatment and the main sites are in the bladder bed and pelvic nodes. Metastases can also occur in distant nodes, lungs, bones and liver (Skinner, 1980; Raghavan, 1985).

In an effort to improve the long-term survival for patients with deeply invasive bladder cancer, we initiated a treatment programme in 1981 in which intravenous cisplatin was administered before definitive treatment. The rationale for this approach has been described in detail previously (Raghavan *et al.*, 1984; Raghavan, 1985).

We present an update of the initial experience in 70 patients and provide further survival data on the first group of 50 patients (treated before December 1983).

Patients and methods

All patients underwent an extensive non-invasive staging protocol, including CT scan and cystoscopy, biopsy and examination under anaesthesia (EUA) (Raghavan *et al.*, 1985). Tumour staging was classified according to the criteria of the UICC. CT scans alone were not used to stage a tumour, *i.e.* they were used only to confirm clinical staging.

Intravenous cisplatin (100 mg/m^2) was administered on day 1 and day 22 of the programme; the dose was reduced to 80 mg/m^2 for patients with serum creatinine 1.3 times greater than normal. An aggressive hydration regimen was used to reduce nephrotoxicity and this required close nursing and medical supervision to avoid fluid overload (Raghavan *et al.*, 1984). Anti-emetics, including haloperidol, dexamethasone and lorazepam, were used liberally to reduce nausea and vomiting (Friedlander *et al.*, 1983). Cystoscopy, biopsy and EUA were repeated 10 to 14 days after the second dose of cisplatin to assess response. Improvement only on the basis of a CT scan was not a criterion of response.

Patients subsequently received their "definitive" treatment as initially planned by the referring urologist: 55 patients were treated with radical radio-

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therapy alone (45-50 Gy to the true pelvis with a 10-15 Gy boost to the bladder, over 5-6 weeks); 15 patients underwent cystectomy, usually preceded by radiotherapy. Patients who showed complete or partial remission at check cystoscopy after cisplatin were eligible to receive two extra cycles of cisplatin (100 mg/m^2 *q* 3-weekly) after completion of definitive treatment.

There are no well defined criteria for the non-invasive evaluation of response to the treatment of non-metastatic bladder cancer. An important limitation of our study was the use of clinical staging. Nevertheless, objective criteria of remission were defined as reported previously (Raghavan *et al.*, 1985). For statistical evaluation, complete and partial responses were grouped together because of the inaccuracy of clinical staging with respect to complete remission.

Details of the patients are summarised in Table 1. More than 80% were treated at their first or second presentation. A greater proportion of patients with T2 tumours received treatment between November 1983 and November 1984, probably as a result of a better acceptance of the protocol by referring clinicians.

Table 1 Characteristics of Patients

Male: female	54: 16
Mean age/median age/SD	63.5/65/8.2 years
Age range	29-79 years
Smokers (> 10/day)	85%
Analgesic abusers	25%
Renal tract non-function/obstruction	50%
Prior radiotherapy	0
Prior chemotherapy	0
Predominant TCC	100% (100%)*
Grade III	78% (88%)*
T3 category	50% (62%)*
T4 category	21% (24%)*

* Figures in parentheses refer to the first 50 patients treated, as previously reported (Raghavan *et al.*, 1985).

Results

Response

Forty patients (57%) showed objective evidence of response to first-line cisplatin, 24 had stable disease and 4 were not evaluable (due to assessment by different urologists before and after chemotherapy). Tumour progression during treatment was demonstrated in two cases. Fifty-nine patients (84%) showed evidence of objective response after completion of their definitive treatment.

Survival

Our data remain preliminary with respect to survival. However, some information is available on the first group of 50 patients. By May 1984, the median survival was 20+ months (range 3-44+), with a 2-year actuarial survival rate of 64%. Twenty-two of the first 50 patients have died, including one death from intercurrent disease (with no evidence of tumour), one patient who died suddenly, probably of pulmonary embolus (included as a tumour-related death) and another who died shortly after salvage cystectomy. Eighteen of these deaths occurred within 18 months of entry into the study. Among the first 50 patients, tumour-related deaths occurred in two patients with T2 tumours, 13 with T3 and six with T4 tumours.

Toxicity

In general, the treatment was well tolerated (Table 2). The major auditory problems included transient high tone hearing dysfunction, tinnitus and audiogram changes. None of the patients with renal toxicity had significant long-term renal dysfunction and dialysis was not required.

There was no evidence that the use of cisplatin compromised the dosage or administration of radiotherapy and there were no unusual post-

Table 2 Toxicity

Side effects	*No. of patients*
Nausea	65
Vomiting	60
Auditory	8
Renal	8
Colitis (chronic post-RT)	6
Diarrhoea	5
Myelosuppression	5
Infection	2
Cystitis (chronic post-RT)	2
Haematemesis	1
Stomatitis	1
Dehydration (diabetic)	1
Inappropriate antidiuretic hormone	1
Subendocardial infarct	1
Atrial fibrillation	1
No toxicity	1
Total	70

operative complications in those patients undergoing cystectomy as part of their treatment. There were no treatment-related deaths, apart from the patient who died after salvage cystectomy. However, of some concern is the possibility of increased damage to normal tissue due to the combination of radiotherapy and cisplatin (Luk *et al.*, 1979). Six patients developed chronic proctitis as a late complication but none has required colostomy and the symptoms have been controlled conservatively. However, two of these patients have suffered recurrent subacute bowel obstructions.

Patterns of relapse

Thirty of the first 50 patients have suffered relapses to date, including 24 with only local recurrence. Five of these relapses consisted only of superficial transitional cell carcinoma (TCC). Distant metastases were noted in bone, lung, lymph nodes, liver, vagina, brain, skin and abdomen. The management of these relapses will form the basis of a subsequent report.

Discussion

Our study continues to show substantial activity of first-line intravenous cisplatin in the treatment of invasive transitional cell carcinoma of the bladder. We observed a 57% response rate to cisplatin and an 84% response rate after definitive treatment. Similar data have been reported by Herr *et al.* (1983) and Soloway *et al.* (1981), although few long-term follow-up details have been provided in these series and the numbers have been smaller.

However, we have demonstrated frequent relapses with the increased passage of time from entry into the study. It is interesting to note that most relapses occurred in the bladder or pelvis, implying a failure to control local disease. Of 24 patients with local progression, 5 had only superficial tumour (each of whom previously had invasive TCC). This may suggest an altered natural history of the disease in selected patients, but further follow-up is required.

Our patients constituted a high risk group, with adverse prognostic features such as advanced age, high tumour grade and stage and ureteric obstruction. Although this study was not randomised, the data suggest a *possible* survival benefit when compared with other reports in the literature. However, in view of the prevalence of relapses and immature survival data, a randomised study must be completed to assess the true value of this approach to treatment. We have begun a multi-centre study in which patients are randomised to receive either two doses of cisplatin followed by 60 Gy radiotherapy versus 60 Gy radiotherapy alone. Similar studies are planned by others to assess the possible benefits of first-line intravenous cisplatin on the results of radical cystectomy.

Although the results obtained with the recently reported regimen "MVAC" for metastatic transitional cell carcinoma are of great interest (Sternberg *et al.*, 1984), the data have not been confirmed and will require further study before the introduction of this regimen into the routine management of non-metastatic disease, particularly in view of the substantial toxicity reported.

It is important to emphasise that primary chemotherapy has not yet been proven in the management of invasive non-metastatic bladder cancer.

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The Authors

B. S. Pearson, FRCS, FRACS, Visiting Urologist and Chairman, Urological Cancer Research Unit.

D. Raghavan, PhD, FRACP, Oncologist and Research Director, Urological Cancer Research Unit.

Requests for reprints to: D. Raghavan, Urological Cancer Research Unit, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia.

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The Role of Endoscopic Treatment after Radical Radiotherapy for Invasive Bladder Cancer

G. SMITH, P. M. QUILTY, W. DUNCAN, G. D. CHISHOLM, J. E. NEWSAM and T. B. HARGREAVE

University Departments of Surgery/Urology and Radiation Oncology, Western General Hospital, Edinburgh

Summary—In a 6-year period 232 patients were treated by radical radiotherapy for transitional cell cancer of the bladder. Fifty-eight patients had secondary surgical management to control either locally persistent or recurrent tumour. Endoscopic treatment alone was used in 31 patients with down-staged tumours and the survival of this group compared favourably with that of 27 patients selected for salvage cystectomy (5-year survival rate 88% *cf.* 44%). A group of patients with favourable prognostic factors may be identified in whom cystectomy can be avoided without prejudice to survival.

The 5- and 10-year survival rates after radical radiotherapy for invasive bladder cancer vary from 25 to 38% (Blandy *et al.*, 1980; Goodman *et al.*, 1981; Hope-Stone *et al.*, 1981). These rates are similar to those reported after primary cystectomy or after a combination of pre-operative radiotherapy and elective cystectomy (Prout, 1976; Wallace and Bloom, 1976; Whitmore, 1981; Skinner *et al.*, 1982; Smith *et al.*, 1982). The advantage of radical radiotherapy is that bladder function may be retained in those who respond to irradiation. Whatever the form of primary management, metastases remain a major cause of death. The stage of tumour at cystectomy is the major factor determining survival. Several authors also highlight the prognostic significance of tumour down-staging at the first cystoscopy after both pre-operative and radical radiotherapy (Blandy *et al.*, 1980; Bloom *et al.*, 1982).

We reviewed our experience over a 6-year period to determine whether a survival advantage may be demonstrated when recurrent tumours have been sufficiently down-staged by radiotherapy to permit endoscopic management instead of salvage cystectomy.

Patients and Methods

From 1978 to 1984, 393 patients with bladder cancer were assessed jointly by urologists and radiation oncologists at a special weekly endoscopic session. Patients were normally assessed under general anaesthesia by cystourethroscopy and bimanual examination. Spinal anaesthesia was required for a few unfit patients. Definitive resection was carried out when possible and biopsies taken of the cancer, any urothelial abnormality and from non-tumour bearing urothelium. Tumour assessment was by the TNM system (UICC, 1978). The histology was reviewed weekly at a clinicopathological meeting of pathologists, urologists and radiation oncologists before deciding the classification of the tumour and further management. Tumours were graded according to the WHO system (Mostofi *et al.*, 1973). Muscle invasion on histology or the persistence of a mass following resection of tumour were the main reasons for selection for radical radiotherapy. Patients with poorly differentiated tumours and superficial tumours beyond endoscopic control were also considered for primary radiotherapy.

Before radiotherapy, patients were investigated biochemically and radiographically for the presence of liver, bone and chest metastases.

Radiotherapy was given using a three-field beam

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directed technique with small fields to cover the bladder and perivesical tissue. The target absorbed dose was normally 55.0 Gray delivered in 20 fractions over 4 weeks. The first cystoscopy was carried out 6 months after radiotherapy with regular cystoscopic follow-up thereafter. The patients were also reviewed in the radiation oncology clinic. Apart from inspection for tumour and any urothelial abnormality, the severity of late irradiation reactions was recorded and the bladder capacity measured. Any suspicious area was biopsied. Bimanual examination under general anaesthesia was always performed to assess muscle invasion, extravesical spread, the mobility and the size of the recurrent cancer. Whenever possible, definitive resection of persistent tumour was performed.

The choice between salvage cystectomy and further endoscopic management depended on many factors. The decision was influenced by the histological confirmation of recurrence, its histological type, grade and evidence of muscle invasion. The size of the tumour and its mobility was taken into account, together with the bladder capacity and evidence of widespread field change in the urothelium. Renal function and changes on intravenous urography were considered; both clinical and radiological assessments were carried out to exclude distant metastases. The patient's symptoms, age, previous medical history and general condition also influenced the decision. The choice of management was finally determined by the informed consent of the patient.

Survival rates are reported from the date of referral to radiotherapy. The life tables with log rank significance levels were calculated as described by Peto *et al.* (1977). Intercurrent deaths have not been included with tumour or treatment related deaths in determining actuarial survival rates.

Results

Of the 393 patients with bladder tumours assessed (Table 1), 86 were not suitable for radical radiotherapy because of age (>79 years), frailty or a very large tumour mass (>7 cm). A palliative course of radiotherapy was given to 63 patients and 23 were not considered suitable for radiotherapy. Twenty-nine patients referred for radiotherapy by surgeons in district general hospitals had lesions which proved amenable to definitive endoscopic resection. Fifteen patients were managed by either primary cystectomy or pre-operative radiotherapy and elective cystectomy during this time; eight of these had bulky cancers over 7 cm in diameter, four had squamous cancer and three had diffuse carcinoma *in situ*. Pure squamous cancer formed 5.5% of all invasive tumours during this period but has been excluded from this analysis. Twenty-nine patients treated with neutron irradiation were excluded because of the particular problems associated with this treatment (Duncan *et al.*, 1982). Two patients who were younger than average and had metastases at presentation were managed by cytotoxic chemotherapy (Carmichael *et al.*, 1985).

Table 1 Initial Treatment

Endoscopic treatment only	29
No local treatment	23
Palliative X-ray therapy	63
Systemic chemotherapy	2
Primary cystectomy	10
Pre-op X-ray therapy + cystectomy	5
Neutron therapy	29
Radical X-ray therapy	232
Total	393

The remaining 232 patients who had radical megavoltage X-ray therapy for transitional cell carcinoma of the bladder formed the subject of this review. There were 168 male and 64 female patients (ratio 2.6:1) with an average age of 67.5 years. The tumour grade and T category at presentation are presented in Table 2. Only six patients had well differentiated tumours (grade 1) and 174 had grade 3 cancers (75%). The majority were invasive (T2 and T3). There were 30 tumours (13%) which had no clinical or histological evidence of muscle invasion (T1), a proportion similar to that found in other series (Blandy *et al.*, 1980).

Table 2 Tumour Grade and T Category at Presentation

	G1	*G2*	*G3*	*T1*	*T2*	*T3*	*T4*
Lasting local control	—	14	73	9	25	48	5 = 87
Recurrence treated by endoscopic methods	2	11	18	9	6	14	2 = 31
Recurrence treated by salvage cystectomy	1	5	21	4	8	14	1 = 27
Progression, unfit, diversion	3	22	62	8	10	55	14 = 87
Total	6	52	174	30	49	131	22 = 232

Four categories of response to primary radiotherapy and subsequent management can be described. The life tables for these groups are presented in Figures 1 and 2.

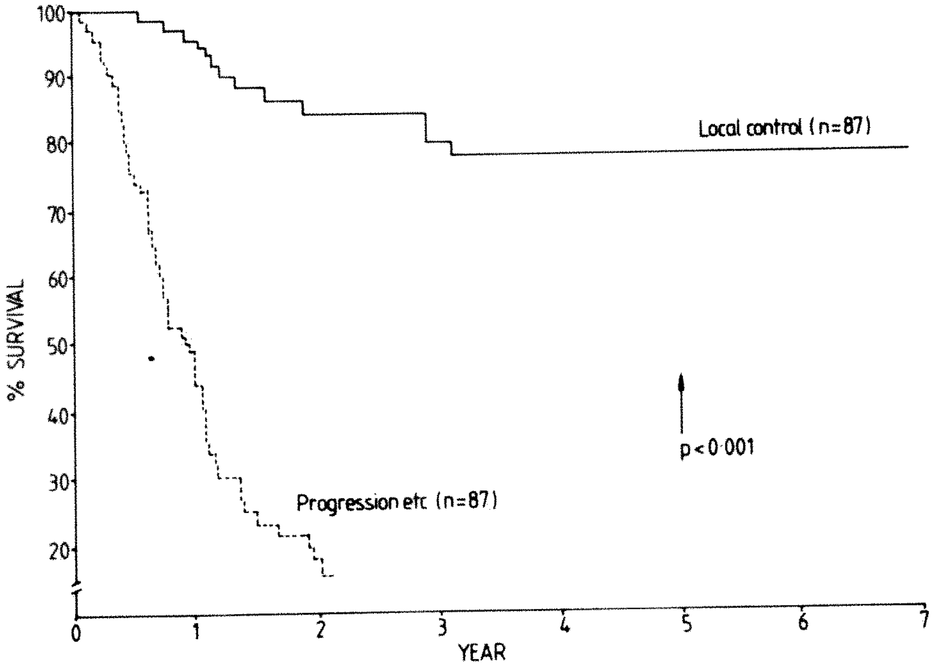

Fig. 1 Life table for patients achieving lasting local control of bladder tumour versus those with progression or clinical deterioration.

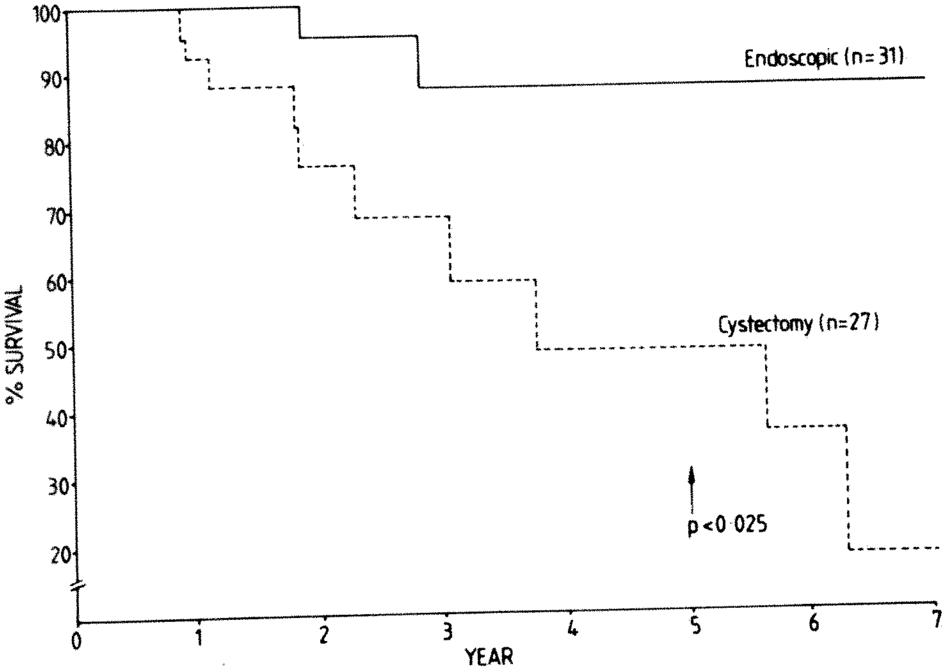

Fig. 2 Life table for patients treated by endoscopic methods versus those selected for salvage cystectomy.

(*i*) *Lasting Local Tumour Control*

Eighty-seven patients had lasting local tumour control after radiotherapy. Six of these patients had major side effects from irradiation, four of whom required urinary diversion. Six patients had metastases while the bladder remained tumour-free. Ten patients died of intercurrent disease. The 5-year actuarial survival from referral to radiotherapy for this group of patients was 78%.

(*ii*) *Persistent or Recurrent Tumour Treated Endoscopically*

Thirty-one patients had persistent or recurrent tumour after radiotherapy and were managed by transurethral resection or cystodiathermy (Table 3). Nine patients had no tumour at the first cystoscopy 6 months after radiotherapy.

Fourteen patients with T3 cancers were all down-staged by the radiotherapy. Two tumours still showed evidence of muscle invasion (T2) but subsequent cystoscopies showed no tumour. There was one cancer-related death in this group. A patient who initially had a T2 tumour had superficial recurrences which were resected 14 and 19 months after radiotherapy. After a further 15 months (3 cystoscopies) without evidence of local tumour recurrence, this patient died with para-aortic lymph node and liver metastases. Three further patients have died from intercurrent disease. The 5-year actuarial survival was 88.6% for the whole group and 100% for those patients initially having T3 tumours.

Tumour control was generally readily achieved. Two patients with refractory tumours received intravesical chemotherapy in addition to resection of tumour.

(*iii*) *Persistent or Recurrent Tumour Treated by Salvage Cystectomy*

Twenty-seven patients were managed by salvage cystectomy. These patients were 6 years younger on average than those treated by endoscopic methods (61.7 *vs* 67.9 years). The distribution of the initial histological grading and T categories was similar to the endoscopically treated group (Tables 3 and 4). Nine of these patients were also free from tumour at the first cystoscopy at 6 months. Three patients had a period of endoscopic control, prior to cystectomy, that lasted between 24 to 36 months. All three patients are alive and tumour-free 8 to 29 months after cystectomy. All other patients had their cystectomy performed shortly after recurrence was identified.

Table 3 Recurrent Tumour Treated by Endoscopic Methods

		Pre-radiation				
		T1	*T2*	*T3*	*T4*	*Total*
Recurrence	T1	8	6	13	2	29
	T2	1	—	1	—	2
Total		9	6	14	2	31

Table 4 Recurrent Tumour Treated by Salvage Cystectomy

		Pre-radiation				
		T1	*T2*	*T3*	*T4*	*Total*
At cystectomy	No tumour	—	—	1	—	1
	pT1	2	5	5	1	13
	pT2	—	1	1	—	2
	pT3	1	2	4	—	7
	pT4	1	—	3	—	4
Total		4	8	14	1	27

Of the 14 patients found to have tumours down-staged at cystectomy two have died with metastatic disease. A further two patients died in whom late irradiation complications were thought to be the main cause of death (Table 5). Five of the 13 patients not down-staged after cystectomy died with metastases. There was one post-operative death and two patients died with pelvic irradiation-induced complications. Much of the longer survival seen in the patient with down-staged cancers is accounted for by the longer interval between radiotherapy and salvage cystectomy in this group compared with those not down-staged.

There were 14 patients who presented with T3 tumours in this group and seven of these were not down-staged at the time of cystectomy (Table 6). Only three of these seven remain alive. Of four patients who died, three had metastatic disease and one died from irradiation-related bowel complications.

The 5-year actuarial survival rate of the patients treated by salvage cystectomy is 44.1% for the whole group and 34.2 for those patients initially having T3 cancers.

(*iv*) *Local Progression, Metastatic Disease or Deteriorating General Condition*

Eighty-seven patients (36% of those starting radiotherapy) were considered unsuitable for

Table 5 Response to Treatment

Response to treatment		*Numbers*	*Intercurrent deaths*	*Tumour deaths*	*Irradiation deaths*	*Five-year survival*
Endoscopic treatment	Down-staged	21	4	1	0	88.6%
	Not down-staged	10	0	0	0	
Salvage cystectomy	Down-staged	14	1	2	2	44.1%
	Not down-staged	13	2	5	2	

Table 6 T3 Cancer Prior to Radiotherapy and Down-staging

	Endoscopic	*Cystectomy*
Number	14	14
Down-staged	14	7
Intercurrent deaths	3	0
Tumour deaths	—	6
Radiation deaths	—	2
5-year survival	100%	34.2% NS

further active local management. Sixteen died within 6 months, mostly of cancer progression. Frailty, inoperable disease and metastases, often in combination, were the main problem. Five patients declined cystectomy (12% of those with operable tumour after radiotherapy). Four patients had a laparotomy and urinary diversion alone owing to unresectable local cancer or the finding of liver metastases. A further seven patients with local tumour recurrence had a urinary diversion with or without formalin instillation of the bladder as a palliative measure. Cystectomy was not performed in these patients because of their poor general condition or severe pelvic fibrosis. The mean survival time of the patients in this group was 11.3 months.

The average age of these patients was similar to that of the patients with lasting local control (68.8 *vs* 69.0 years).

Discussion

Only about 35% of patients can be expected to have lasting local tumour control after radical radiotherapy. Cystectomy is the standard secondary management for residual or recurrent bladder cancer after radical radiotherapy (Blandy, 1985) but there are often over-riding reasons why it may not be performed. In our experience there is another group of patients who have residual or recurrent tumour following radical radiotherapy but are not suitable for curative therapy because of advanced age, poor general condition, the presence of fixed tumour or the development of overt metastases. Some patients may refuse to undergo cystectomy.

This series has shown that definitive endoscopic resection is a remarkably effective form of management in at least half of the patients with residual or recurrent cancer after radiotherapy. In many centres these patients would have been considered for salvage cystectomy. However, not only is endoscopic resection or cystodiathermy much safer, simpler and less expensive, but it also preserves bladder function and, most importantly, does not prejudice prognosis. Indeed this analysis has shown that by careful selection the survival of our patients managed by endoscopic procedures was significantly better than those who had a salvage cystectomy.

The patients discussed in this paper were managed jointly by urologists and radiation oncologists at the Western General Hospital. This hospital is also the regional radiation centre and the total experience of the Department of Clinical Oncology has recently been published (Quilty *et al.*, 1985). There are some striking differences in that the endoscopically treated group had a lower (48%) 5-year survival rate than those treated by salvage cystectomy (62%). This difference is partly explained by variation in selection between contributing hospitals. Also, the actuarial methods used for the overall series included intercurrent deaths and no age correction was applied. In both series the endoscopically treated patients were 6 years older than the cystectomy group and therefore losses by intercurrent death can be expected to have a more marked effect on the survival in the endoscopic group.

Our experience suggests that patients who have residual or recurrent pTa or pT1 cancer may reasonably be managed by secondary endoscopic surgery. In addition, two patients successfully treated endoscopically were found to have pT2 cancers. By being selective, a group of patients can be identified in whom survival after endoscopic management is good. This may be explained by the selection of patients with favourable prognostic features such as reduction in T category after radiotherapy or an initial low T category before radiotherapy. Definitive endoscopic management of suitable tumours may achieve disease-free survival rates comparable to salvage cystectomy while preserving bladder function.

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The Authors

G. Smith, FRCS, Urological Registrar.
P. M. Quilty, FRCR, Senior Registrar.
W. Duncan, FRCR, MRCP, FRCP, FRCS, Professor of Radiation Oncology.
J. E. Newsam, FRCS, Consultant Urologist.
G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery.
T. B. Hargreave, MS, FRCS, FRCSE, Senior Lecturer.

Reprint requests to: G. Smith, Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Histochemical Changes after Ureterosigmoidostomies and Colonic Diversion

J. R. STRACHAN, H. C. REES and GORDON WILLIAMS

Institute of Urology, Department of Histopathology and Department of Surgery, Royal Postgraduate Medical School, London

Summary—Forty patients with colonic urinary diversions were studied for morphological and histochemical changes in the colon using haematoxylin and eosin, and high iron diamine alcian blue stains. Eighty-nine per cent of ureterosigmoidostomies biopsied at the ureteric orifice and 44% biopsied distal to the orifice showed "transitional" changes thought to represent a pre-malignant state. Thirty-eight per cent of patients who had had ureterosigmoidostomies in the past and 100% of the colon conduits also demonstrated this change. The earliest "transitional" change occurred 1 year after the diversion. This and the low incidence of morphological changes in this group of patients suggest that the finding of "transitional" mucosa is of no value in the follow-up of patients with colonic urinary diversions.

The first case of adenocarcinoma complicating urinary diversion into the colon occurred at the site of anastomosis between the trigone and colon (Hammer, 1929). Subsequently another 19 patients who had diversions for benign conditions have developed adenocarcinoma of the colon (Charron and Delisle, 1982; Sacré *et al.*, 1983).

The colonic mucosa contains mucin which consists of conjugated glycoproteins. The acid glycoproteins found in the colon are sialomucins and sulphomucins. The normal pattern within the sigmoid colon is sulphomucin within the lower two-thirds of the crypt with some sialomucin in the upper third. "Transitional" mucosa in which sialomucin predominates throughout the length of the crypt has been found adjacent to adenocarcinoma of the colon and for varying distances from it (Filipe and Branfoot, 1976). Studies in rats have shown that when tumours have been induced with carcinogens, "transitional" change is a pre-malignant event.

Patients and Methods

Forty patients who had had colonic diversions were examined to obtain colonic mucosa. The colonic biopsy specimens were taken with biopsy forceps via either a rigid sigmoidoscope or colonoscope.

Group a Nineteen patients with ureterosigmoidostomies performed for benign conditions at a mean age of 16.6 years (range 1-57) were examined with a colonoscope and biopsied near the ureteric orifices, which were identified by using intravenous methylene blue. Their diversions had been present for a mean of 22 years (range 5-38).

Group b Nine patients with ureterosigmoidostomies performed for malignant conditions were examined with a rigid sigmoidoscope and random biopsies were taken 13 cm from the anal margin. The mean age at operation was 64.7 years (range 57-74). The mean duration of the ureterosigmoidostomy was 9.4 years (range 1-26).

Group c Eight patients had ureterosigmoidostomies which were later converted to another form of diversion. Biopsies were taken via a colonos-

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Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

cope near the site of the ureteric orifices. The average time before conversion was 10.4 years (range 8-18) and after conversion 12.6 years (range 8-18). The average age at the initial operation was 14.8 years (range 3-47) and overall time to biopsy 24.5 years (range 12-37) after the first operation.

Group d Four patients had urinary diversion into a colon conduit. Biopsies were taken both from the colon conduit and the sigmoid colon. The mean age at operation was 9.3 years (range 2-14), and the average length of time with the conduit was 17.5 years (range 5-24).

The colonic biopsy specimens were placed in 10% formol saline solution and were later stained with haematoxylin and eosin (H and E) and also with high iron diamine alcian blue pH 2.5 (HID-AB) (Spicer, 1965).

The specimens were examined by one of us (HCR) for morphological changes with H and E and histochemical changes with HID-AB.

Results

The mucins in the colonic mucosa were differentiated by staining with HID-AB. This technique stains sialomucin blue and sulphomucin brown. The colonic mucosa was classified as "transitional" if more than 50% of cells within a crypt stained blue and more than 50% of cells within the lower zone of the crypt stained blue.

Group a All of the slides examined with H and E were morphologically normal. When examined with HID-AB, 17 of 19 demonstrated a "transitional" pattern. Two patients had normal mucins, one had had a previous bowel resection for adenocarcinoma at the ureteric orifice after 18 years with the biopsy taken 11 years later, and the other had had a previous local bowel resection for adenoma.

Group b H and E staining revealed one tubuloadenoma, while the other eight were morphologically normal. HID-AB showed a "transitional" pattern in four patients, including the patient with the tubuloadenoma. In one patient "transitional" change had occurred within 1 year of diversion. The other five patients had a normal mucin pattern.

Group c One H and E specimen revealed an adenocarcinoma discovered 26 years after the original operation and 22 years since re-diversion, while the other seven had normal morphology. HID-AB showed a "transitional" pattern in three patients, including the patient who had the tumour discovered at biopsy at 26 years. The second of these had had an adenocarcinoma and colectomy at 26 years with the biopsy 11 years later, and the third had the biopsy at 12 years but had no morphological abnormality. One of the five patients with normal mucins had had a previously resected adenocarcinoma.

Group d The H and E biopsies of both the conduit and the colon were normal. The HID-AB showed all four to have a "transitional" pattern in the conduit with a normal pattern within the colon.

Discussion

Ureterosigmoidostomy increases the risk of developing a tumour in the colonic mucosa (Stewart *et al.*, 1982). Following ureterosigmoidostomy, benign polyps occur on average 22.4 years later, and adenocarcinomas at 27 years. Eight reported patients have had re-diverted ureterosigmoidostomies with tumour formation on average 26 years later, which is similar to those with continuous ureterosigmoidostomies (Spence *et al.*, 1979). There have been two reports of tumour within colon conduits (Chiang *et al.*, 1982; Wilson and Morales, 1982).

Various theories have been put forward for tumour formation in ureterosigmoidostomies: altered bowel mechanics (Tank *et al.*, 1973), the age of the anastomosis (Carswell *et al.*, 1976), the irritative effect of urine (Urdaneta *et al.*, 1966), or the high concentration of electrolytes (Haruindey *et al.*, 1973). A mixture of urine and faeces produces N-nitrosamines, which are known to be carcinogenic (Stewart *et al.*, 1981). Chiarelli and Sandei (1984) suggested that these tumours are urothelial in origin and develop from glandular metaplasia of the ureteric stumps. Leadbetter *et al.* (1979) suggested that urine could still be the cause of tumour formation in "dry" stumps due to the long doubling time of colonic tumour cells.

Histochemical changes are present before there is morphological evidence of atypia and represents pre-malignant change in "transitional" mucosa (Filipe and Branfoot, 1976). However, early morphological changes, such as lengthening of the crypts, dilatation or branching, may not be regarded as atypia. Isaacson and Attwood (1979) suggested that the histochemical changes were secondary to the tumour and not pre-malignant transformations.

In group (a), "transitional" mucosa was present in 17 of 19 patients, but the only tumour in this group did not appear until 18 years after the original operation. The two patients with normal mucin patterns had had previous surgery for tumours some years before. In group (b), "transitional" mucosa was found in four of eight patients and the mean duration of the diversion was only 9.4 years. One patient in this group had developed "transitional" change within 1 year of diversion. In group (c), three of the eight patients developed adenocarcinomas. One was found at the time of biopsy and associated with "transitional" change; of the two patients who had had previous surgery, one had "transitional" change and the other normal mucins. In group (d), all patients showed "transitional" change in the colon conduits. Their sigmoid colon biopsies showed normal mucin stains.

The finding of "transitional" mucosa in 75% of our patients is of considerable interest. The appearance of this change within 1 year of diversion, and the finding of "transitional" change some distance from the site of ureteric implantation (group b), suggests that this is not a pre-malignant change but is due to the irritative effect of urine. Once this change has been induced it persists (group c). If it was a pre-malignant condition one would expect carcinomas to occur throughout the left colon and not just at the site of the ureteric implants. "Transitional" mucosa cannot be considered a predictor of tumour development and routine staining of biopsies for "transitional" changes cannot be advocated.

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The Authors

J. R. Strachan, FRCS, Research Registrar, Institute of Urology.

H. C. Rees, FRCPA, MRCPath, Senior Registrar, Department of Histopathology, Hammersmith Hospital and Royal Postgraduate Medical School.

Gordon Williams, FRCS, Consultant Urologist, Department of Surgery, Hammersmith Hospital and Royal Postgraduate Medical School.

Requests for reprints to: J. R. Strachan, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Transurethral Incision of Prostate (TUIP): 646 Cases in 15 Years—a Chronological Appraisal

A. ORANDI

John W. Draper Research Laboratory, Fergus Falls, USA

Summary—Transurethral incision of the prostate was performed on 646 patients in 15 years. This operation is offered as a surgical cure for bladder outlet obstruction in men of all ages and different sized prostates. In large glands TUIP may not be desirable. Deep incisions cause surgical and sexual complications and may fuse by adhesions. In matched cases this method provided better results and fewer complications than the standard transurethral resection.

In 1968 a 31-year-old man suffered bladder outlet obstruction and persistent infection. After months of unsuccessful conservative management, his prostate was resected. The obstruction and infection subsided but the patient became sterile and experienced loss of sexual vigour and pleasure. It was assumed that resection and scarring of the prostatic urethra were responsible and that a less traumatic operation would have entailed fewer complications.

In 1964, Aboulker and Steg reported a 75% success rate with divulsion of the prostate to relieve bladder outlet obstruction. Unfortunately, profuse bleeding, incontinence and infection occurred frequently. It appeared that controlled rupture of the prostatic urethra by endoscopic incisions in predetermined locations would eliminate obstruction and avoid untoward complications. Thus in 1969, in a 51-year-old with early prostatic enlargement and obstruction, the bladder neck and the prostatic urethra were enlarged by deep incisions at the 5 and 7 o'clock positions. The patient remains well 15 years later.

Initially, transurethral incision of the prostate (TUIP) was considered suitable mostly for younger men with prostatism and early prostatic enlargement. The early results in selected cases were excellent (Orandi, 1973) and the operation was then applied to patients of all ages with larger prostates. TUIP was compared with the standard transurethral resection of the prostate (TURP) by Orandi (1978). The results favoured TUIP. However, comparative data, even from randomised series, included unmatched cases, *i.e.* the outcome of resection of a large prostate causing obstruction was compared with that of incision of a small prostate for obstructive symptoms of obscure origin. Accordingly, from 1982 to 1984, 100 TUIP candidates were alternately managed by incision and resection operations (Orandi, 1985). The overall results of TUIP were better than those of TURP.

Patients and Methods

Since 1969, 646 men with bladder outlet obstruction have been treated with TUIP and 2120 with TURP (TUIP/TURP ratio 23%). The TUIP patients' ages ranged from 32 to 98 years, with 114 under 60 and 125 over 80 years. The diagnosis was based on subjective symptoms, cystourethrography and at times on routine urodynamics (uroflowmetry, cystometry, electromyography and urethral profilometry).

Of 623 pre-TUIP cystourethrograms, the post-voiding residual was described as: none 30 cases; small 223; moderate 131; large 180, and total 59. Vesicoureteric reflux was present in 38, diverticula and pseudodiverticula in 115, and bladder stones in

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11 cases. Sagging of the bas-fond appeared frequently on the lateral voiding urethrogram. The degree of this "sacculation" correlated well with the extent and duration of obstruction.

Routine urodynamics (105 cases), although confirming low flow rates, bladder compliance and detrusor status, were not essential in diagnosis or the choice of operation and more detailed testing was not available (Turner-Warwick *et al.*, 1973; Yalla *et al.*, 1981).

The selection of patients for TUIP was based on endoscopy. Endoscopic configurations of bladder outlet depended on the make, size, shape, location and direction of the instrument and the fullness of the bladder. After analysing over 5000 endoscopic photographs of the bladder outlet with and without obstruction, a standard method of evaluation was established. The bladder outlet was appraised and photographed from three positions: the bladder neck (cervical), mid-prostatic, and from the verumontanum (apical), both with empty and full bladder under approximately 50 cm water pressure (Fig. 1). The patients were under local as well as spinal anaesthesia. When the bladder was empty, every bladder outlet appeared similarly obstructed. When the bladder was full, the appearances varied. Based on these endoscopic appearances and their correlation with the rectal palpation of prostate with and without the scope in the urethra, and the tissue weight in the alternate TUIP-TURP management of 100 TUIP candidates (Orandi, 1985), four types of endoscopic configuration could be described in TUIP candidates (Fig. 2). Intermediate combinations and types were also observed.

Post-operative evaluation included subjective appraisal at intervals of 6 weeks and 3 months, uroflowmetry and cystourethrography. All symptomatic patients and selected patients with no symptoms were subjected to cystography (260), urodynamics (93), cystoscopy (110) and endoscopic photography (75).

Nearly all patients came from the same area, were managed by the author only and followed from 3 months up to 15 years.

A continuous flow rectoscope fitted with a TUIP knife electrode (Greenwald Surgical Co, Lake Station, USA) was inserted through a perineal urethrotomy (Flanagen, 1972) and the bladder was filled under approximately 50 cm water pressure for appraisal, photography and surgery.

In the early cases the incisions, one at 5 and the other at 7 o'clock positions, extended from the ureteric orifice to the side of the verumontanum. They split the bladder neck and the full thickness of the prostate. However, such incisions often perforated the capsule and opened venous sinuses, causing extravasation and venous bleeding. Later, in type I and type II and especially in the young, shallower and shorter incisions were made (Fig. 3). Contrary to the early notions, TUIP was not always a simple, short and easy operation.

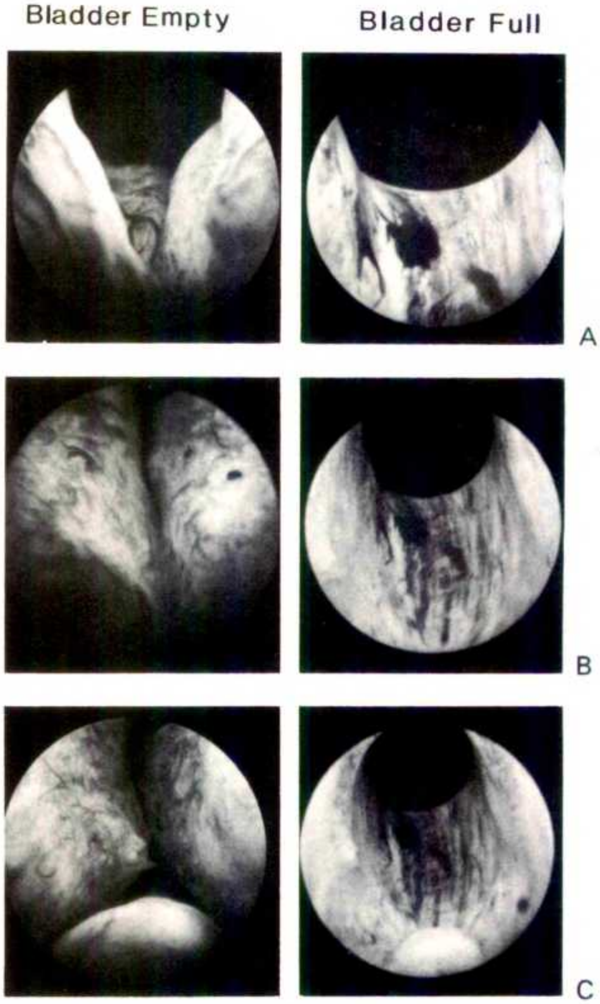

Fig. 1 Bladder outlet is viewed at 3 levels: (A) bladder neck, (B) mid-prostatic, and (C) at the verumontanum, with both empty and full bladder.

Biopsies in 563 cases were obtained with the cutting loop and recently with the "resectoscope biopsy needle" (Greenwald Surgical Co.). They showed benign prostatic hypertophy (BPH) in 50%, prostatitis with BPH (30%), carcinoma (11%), prostatitis alone (7%) and prostatic tissue (2%).

In a few cases incision of the prostate was accomplished by a transvesical endoscopic

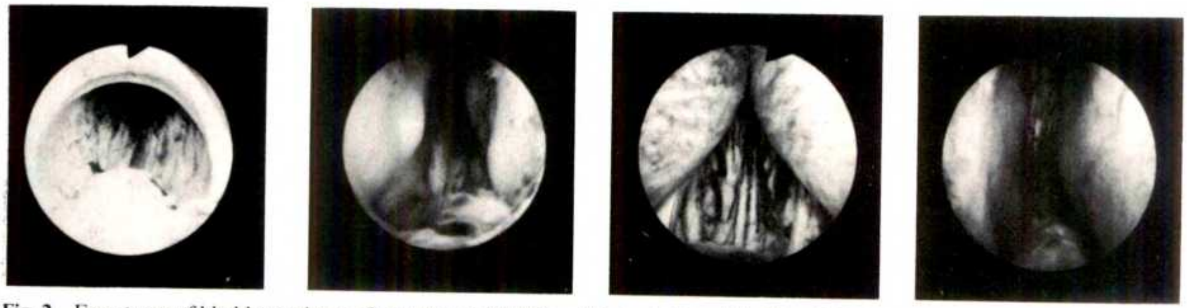

Fig. 2 Four types of bladder outlet configurations in TUIP candidates: left to right: Type I, II, III, IV.

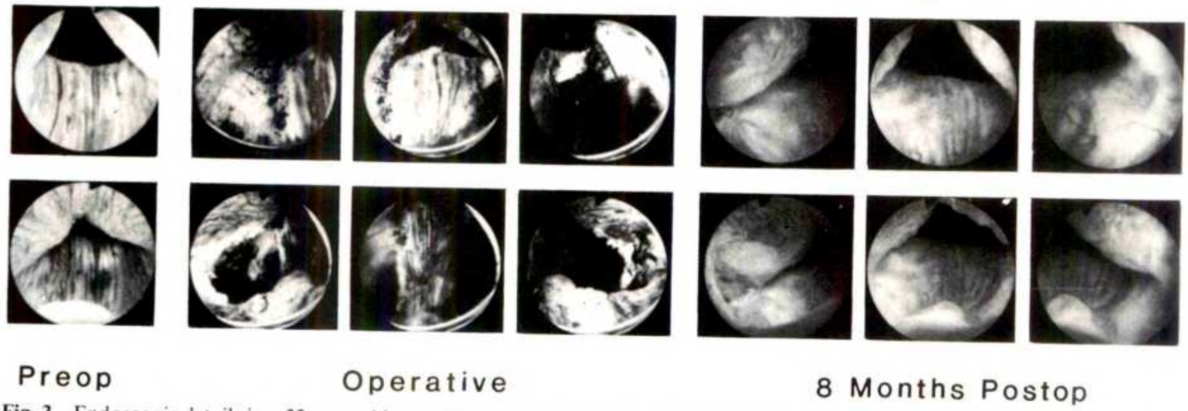

Fig. 3 Endoscopic details in a 32-year-old man. Normal post-operative sexuality and ejaculation (patient has fathered a child after TUIP).

approach. TUIP was also performed selectively under local anaesthesia using the "resectoscope injection needle" (Orandi, 1984).

After surgery, continuous irrigation through a 3-way Foley catheter secured bladder drainage; if bleeding persisted, traction was applied on the catheter with a special traction device (Orandi, 1978). The catheter was removed in 1 to 3 days.

Results

Symptomatic relief was good in 79%, fair in 11% and poor in 10%. Those with good results experienced normal urination and full satisfaction with the operation. Fair results meant partial improvement but no desire for further treatment. In 10% (including 62 re-operations) the outcome was poor, and these poor results persisted in 30 cases even after re-operation.

Comparing 38 consecutive pre- and post-operative uroflowmetry tests, 30 (84%) displayed a better post-operative maximum flow rate. Post-operative voiding cystograms in selective patients with good results revealed considerable improvement in the pre-operative cystographic abnormalities. Even in symptomatic patients, many post-operative cystograms were improved. On follow-up cystoscopy and endoscopic photography in successful operations, the incisions were intact and the median lobe atrophic. However, results could not be assessed by endoscopic evaluation.

Incisions appeared to interrupt the blood supply to the median lobe, causing atrophy. They also opened the obstructed prostatic ducts, drained entrapped prostatic secretions and released many stones.

In 114 post-TUIP patients under 60 years of age, sexuality was better in 15, unchanged in 44 and reduced in 25. Fifteen patients were excluded because of neurological conditions and another 15 had no comments. Ejaculation persisted in 53%.

Complications are listed in the Table, which compares matched and unmatched cases of TUIP *vs.* TURP and the total 15-year series. Sixty-two patients required re-operation (59 resection and 3 re-incision) from 3 months to 11 years after TUIP. In 30, re-operation also failed.

Adhesions in the incisions and even between the

Table TUIP Compared with TURP—Post-operative Complications.

	1969-1979 Unmatched		*1982-1984 Matched*		*1969-1985*
	330 TUIP	*330 TURP*	*50 TUIP*	*50 TURP*	*646 TUIP*
Bleeding	18	16	6	3	28
Retention, temporary	42	35	7	6	73
Transfusions:					
Patients	2	8	0	0	6
Units of blood	6	10	0	0	15
Incontinence:					
Total	0	1	0	0	0
Partial (transient-stress)	0	1	1	3	2
Adhesions					14%
Urethral strictures	3	6	1	5	19
Bladder neck contracture	0	6	0	5	*2
Epididymo-orchitis	5	5	0	3	11
Mortality	4	3	0	1	5
Repeat prostatic surgery	3	6	3	7	62

* Post-TURP contracted bladder neck treated by incision. Contracture recurred.

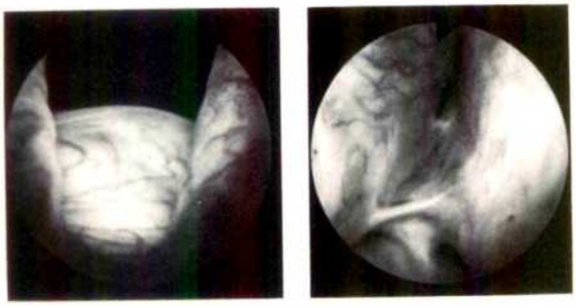

Fig. 4 Post-operative adhesions, non-obstructive.

lateral lobes were observed in 16 of the 110 patients cytoscoped post-operatively (Fig. 4). Nevertheless, only in one case (prostatic carcinoma) was re-operation necessary.

Discussion

Symptoms of bladder outlet obstruction, whether from the bladder neck (Turner-Warwick *et al.*, 1973), the prostatic urethra, or both, without appreciable prostatic enlargement is more prevalent than complained of by the patients as they believe this condition to be rare; the condition is not treated by the urologists because of the fear that definitive surgical management by the standard transurethral resection would result in surgical and sexual complications. Many younger men suffer bladder outlet obstruction long before they develop "detrusor instability" and many older men with overt prostatism are ignored because they have a small prostate. As a result, men of all ages with bladder outlet obstruction and small prostates are subjected to years of ineffective conservative management until either old age, large prostate, or both warrant definitive surgical treatment.

The exact site of the obstruction remained obscure, so that neither the necessary depth and length of the incisions, nor their efficacy in relieving the obstruction, could be assessed while the operation was in progress. These assessments had to be made weeks and months after TUIP. Attempts at a transvesical endoscopic approach, leaving the bladder outlet and the urethra unoccluded for pressure-flow study, were frustrated by lack of compatible instruments and other technical limitations.

Large glands required deep incisions in the capsule. Deep incisions invariably entered venous sinuses and perforated the capsule, causing extravasation and uncontrolled venous bleeding which frequently necessitated extensive fulguration. In these instances post-operative bleeding, temporary urinary retention, erection problems and retrograde ejaculation were not uncommon.

Although the initial expectations from TUIP were not fully achieved, because the surgical and sexual complications did occur, nonetheless, since the introduction of this alternative surgical method, bladder outlet obstruction has been surgically cured without resection of the prostate in many neglected patients and with fewer complications than the standard transurethral resection, thus making definitive surgical cure available to all ages.

Acknowledgments

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The Author

A. Orandi, Private Practitioner in Urology, Fergus Falls; Clinical Professor of Urology, University of Minnesota.

Requests for reprints to: A. Orandi, 615 South Mill Street, Fergus Falls, Minnesota 56537, USA

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TURP Without TURP Syndrome

D. W. GALE and R. G. NOTLEY

Department of Urology, Royal Surrey County Hospital, Guildford

Summary—A series of 500 patients studied retrospectively and prospectively to examine changes in the serum sodium following transurethral resection of the prostate showed no significant incidence of induced hyponatraemia. The TURP syndrome has not been encountered clinically in this department for 10 years, which correlates with the findings of this study. The possible reasons are the habitual use of the irrigating resectoscope, a policy of simplification of management for patients undergoing TURP, and operations being performed only by experienced surgeons.

A syndrome of confusion, hypotension, bradycardia, malaise and collapse during transurethral resection of the prostate was described by Creevy (1947). It had been termed TURP syndrome and in extreme cases led to jaundice and death due to renal failure. This syndrome is associated with acute hypervolaemia and hyponatraemia (Harrison *et al.*, 1956) and is exacerbated and made more dangerous if hypotonic irrigating fluid is used (Norris *et al.*, 1973). The absorption of irrigating fluid from the prostatic fossa is associated with high pressures within that fossa during resection (Madsen and Naber, 1973) and this realisation led to the introduction of the constant irrigation resectoscope (Iglesias *et al.*, 1975).

TURP syndrome remains a constantly occurring, although rare, complication of transurethral resection of the prostate. The description of a prototype ion-selective electrode for constant monitoring of serum sodium during resection (Watkins-Pitchford *et al.*, 1984) prompted the authors to look into the reasons why this syndrome has not been observed in the last 10 years in the Department of Urology in Guildford, where approximately 250 transurethral resections of the prostate are performed *per annum*.

Patients and Methods

Three groups of patients were studied, comprising in all 500 men undergoing transurethral resection of the prostate. All 500 were operated upon by one of the authors (RGN) using a standard Storz 24 F sheath non-irrigating resectoscope for the first 200 patients and subsequently the constant irrigation 26 F sheath manufactured by the Endoscopic Instrument Company, which was designed to take the 24 F electrotome. The method of management outlined by Notley and Schweitzer (1978) was followed. The irrigating fluid used was 1.4% glycine solution. The diathermy machine was a Valleylab SSE2 Solid State electro-surgical apparatus. General anaesthesia was used in most cases, with spontaneous inhalation of nitrous oxide, oxygen and halothane through a face mask on open circuit. Regional anaesthesia, using spinal or epidural anaesthesia, was used for patients with severe respiratory disease. Blood loss was monitored during each operation and intravenous fluids, either colloid or crystalloid, were not administered unless indicated clinically during the procedure. Diuretics were not used.

Two groups, each consisting of 200 unselected consecutive men undergoing transurethral resection, were examined retrospectively. These two groups were studied originally to evaluate the claimed advantages and disadvantages of continuous irrigation during resection compared with the standard intermittent irrigation. These results have been reported elsewhere (Notley, 1982), but the case records have been re-examined to study the changes in serum sodium in these patients.

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The third group comprised 100 patients studied prospectively with the specific purpose of examining the variation in serum sodium immediately before and after transurethral resection of the prostate. The serum sodium in this group was measured in the laboratory using an ion-selective electrode method. The blood samples were taken during induction of anaesthesia prior to the resection and again just as the patient was leaving the theatre to be transferred to the recovery ward.

Results

Details of the resuts of these three groups of patients are summarised in the Table.

Table

	Average	*Range*
GROUP 1: 200 patients—non-irrigating resectoscope		
Age (years)	70.6	(42- 92)
Weight of prostate (g)	28.6	(5- 100)
Blood loss (ml)	241.6	(50-2250)
Serum sodium (mmol/l)—in 172 (86%) of cases		
pre-operative average	142	(138- 146)
post-operative average	140	(132- 145)
(48% showing fall of 2-6 mmol/l		
GROUP 2: 200 patients—irrigating resectoscope		
Age (years)	77.7	(49- 97)
Weight of prostate (g)	31.6	(10- 150)
Blood loss (ml)	238.9	(10-1200)
Serum sodium (mmol/l)—in 160 (80%) of cases		
pre-operative average	144	(140- 146)
post-operative average	142	(136- 146)
(38% showing fall of 1-5 mmol/l)		
GROUP 3: 100 patients—irrigating resectoscope		
Age (years)	76.4	(42- 89)
Weight of prostate (g)	28.5	(10- 120)
Blood loss (ml)	210	(10-1740)
Serum sodium (mmol/l)		
pre-operative average	143	(129- 147)
post-operative average	142	(129- 146)
(60% showing fall of 1-4 mmol/l)		

Discussion

In this survey, groups 1 and 2 suffered from the disadvantage of being studied retrospectively, the particular information being sought not being the object of the original study. Thus in only 86% of group 1 and 80% of group 2 were measurements of serum sodium available post-operatively within 48 h of prostatic resection. Not only are the data in this respect incomplete, but it would have been possible to miss a short-lived period of hyponatraemia. However, the study showed no significant fall in sodium levels in either group and no patient showed clinical manifestations which could be interpreted as even a mild form of TURP syndrome.

In the prospective group, group 3, 60% of patients showed an actual fall in serum sodium level. The ion-selective electrode measures changes of potential difference between its sensor and reference electrodes which are dependent upon sodium ion concentration. It does so within a range of accuracy of plus or minus 2 mmol. In only six patients in group 3 did the serum sodium fall more than 2 mmol and in no patient did it exceed 4 mmol. Statistical analysis with a paired t test showed the probability of a significant difference between the pre-operative and the post-operative sodium levels to be less than 0.001, *i.e.* there was no significant difference.

This survey has shown no significant incidence of post-operative hyponatraemia associated with transurethral resection of the prostate and this correlates with the absence of a clinically detectable case of TURP syndrome. However, it has not answered the secondary question as to why no case of TURP syndrome has occurred. Is some factor in the management of patients undergoing TURP in this hospital responsible?

As far as it is possible to assess from the literature, our patients do as well as elsewhere in the United Kingdom. The mortality rate is 0.5%. The incidence of infective, embolic and other cardiorespiratory complications compares well (Notley, 1982). The weight of prostate resected, averaging 29.5 g, matches other series, so not only small glands are being resected transurethrally.

There are three areas in which particular care is taken in this department. First, it has been demonstrated by example and careful documentation that the intra-operative blood loss during transurethral prostatic surgery rarely warrents replacement and, thus, the routine intravenous infusion in an elderly patient with combinations of chronic cardiorespiratory disorders has been abolished. Only four patients in group 3 required intravenous infusion, three to replace blood lost during a long resection of a large gland and one who became hypotensive after his spinal anaesthetic. There is therefore no risk of inducing hyponatraemia in these patients by the infusion of dextrose solutions of any kind. By the same token, diuretics are not used post-operatively.

The second area is the habitual use of the constant irrigation resectoscope, so that the rise of pressure within the prostatic fossa incriminated by Madsen and Naber (1973) is avoided.

The third area is the type of anaesthesia used, with minimal or no pre-operative medication and the use of general anaesthesia without endotracheal intubation (unless essential to maintain an airway) and without intermittent positive pressure respiration. Regional anaesthesia using spinal or epidural anaesthesia was used for patients with severe respiratory problems.

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The Authors

D. W. Gale, MB,ChB(Cape Town), Senior House Officer.
R. G. Notley, MS, FRCS, Consultant Urologist.

Requests for reprints to: R. G. Notley, Department of Urology, Royal Surrey County Hospital, Egerton Road, Park Barn, Guildford, Surrey GU2 5XX.

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Biochemical Markers and Skeletal Metabolism in Carcinoma of the Prostate

Use of Decision Matrix Theory and ROC Analysis

G. H. URWIN, R. C. PERCIVAL, A. J. P. YATES, M. E. WATSON, M. COUCH, B. McDONALD, A. R. W. FORREST, J. L. WILLIAMS and J. A. KANIS

University Department of Human Metabolism and Clinical Biochemistry, and Departments of Clinical Chemistry and Urology, Royal Hallamshire Hospital, Sheffield

Summary—The discriminative ability of several skeletal and tumour markers was assessed in 102 patients with prostatic disease. These comprised serum acid and alkaline phosphatase, serum albumin and osteocalcin, urinary excretion of calcium, hydroxyproline and 6-oxo prostaglandin $F_1\alpha$. None of the tests was of value in distinguishing patients with benign prostatic disease from those with tumour not involving the skeleton. Values of serum osteocalcin, urinary excretion of calcium and urinary 6-oxo prostaglandin $F_1\alpha$ failed to discriminate significantly between patients with or without metastases. The remaining four markers were compared by decision matrix analysis and receiver operating characteristic (ROC) curves. Serum alkaline phosphatase provided the most sensitive marker of skeletal metastases (80.5%), followed by serum acid phosphatase (80%), hydroxyproline (68%) and albumin (30%). ROC analysis suggested that alkaline phosphatase conformed most closely to the "ideal marker" with highest specificity and sensitivity.

Biochemical markers of tumour activity have been used in prostatic cancer to stage the disease and monitor the effects of treatment. The most widely used is acid phosphatase, but alkaline phosphatase and urinary excretion of hydroxyproline have been used to assess the presence or absence of skeletal metastases. It has been suggested that urinary hydroxyproline may be a more useful marker than acid or alkaline phosphatase (Bishop and Fellows, 1977; Hopkins *et al.*, 1983), although hydroxyproline may be derived from tumour tissue as well as skeletal collagen degradation. Similar claims have been made for prostacyclin in prostatic cancer (Khan *et al.*, 1982).

The value of markers of disease activity is dependent in part upon their sensitivity and specificity. We have evaluated the relative performance of these markers in discriminating between patients with metastases and those without. In addition, we assessed the fasting calcium excretion, an index of net calcium release from bone (Grainger *et al.*, 1984) and serum osteocalcin, a bone-specific protein synthesised by osteoblasts (Price *et al.*, 1976).

Patients and Methods

Eighty-nine patients with prostatic carcinoma confirmed by tissue histology were studied. Patients were divided into those with (n = 72) or without (n = 17) skeletal metastases as judged by bone scintigraphy. An additional 13 patients with benign prostatic hyperplasia served as controls. After a 12-h overnight fast, the bladder was emptied and the subsequent urine was collected over a 2-h period (fasting urine). A serum sample was obtained by venepuncture midway through this period.

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

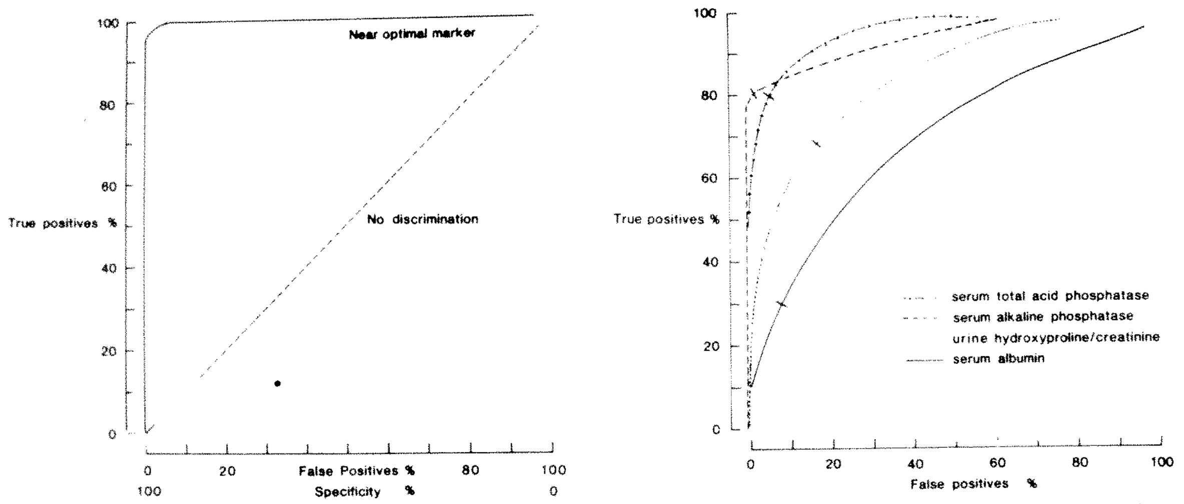

Fig. Hypothetical ROC curves (left) compared with observed data (right) using four markers of disease activity in 102 patients with prostatic disease. Each curve is marked with a point (/) which denotes the specificity and sensitivity of each test at the upper limit of the normal range for that marker (lower limit in the case of albumin).

Serum albumin and total alkaline phosphatase were measured using a Technicon SMAC. Total serum acid phosphatase was measured by a standard colorimetric method using a Roche Diagnostica COBAS Bio centrifugal analyser with 1-naphthyl phosphate as substrate. Urinary calcium was measured by atomic absorption spectroscopy and urinary hydroxyproline by the method of Stegeman and Stalder (1967). The stable metabolite of prostacyclin, 6-oxo-prostaglandin $F_1\alpha$, was measured in urine by radioimmunoassay after separation by high performance liquid chromatography (Jones and Russell, 1983). Serum osteocalcin was measured by radioimmunoassay using an antibody raised in rabbits against purified bovine osteocalcin (Beresford *et al.*, 1984). Urinary excretion of hydroxyproline, 6-oxo prostaglandin $F_1\alpha$ and calcium were expressed as ratios to creatinine excretion.

The significance of differences between mean values was computed using Student's *t* test (two tailed) after logarithmic transformation where appropriate. The ability of each test to distinguish between patients with and without skeletal metastases was evaluated using decision matrix analysis and receiver operating characteristic (ROC) curves (McNeil *et al.*, 1975; McNeil and Adelstein, 1976).

The decision matrix analysis categorised patients according to whether skeletal metastases were present or absent and whether the diagnostic test was normal or abnormal. Thus patients fell into four categories: an abnormal test when skeletal disease was present (a), a normal test when disease was present (b), an abnormal test with no skeletal disease (c), and a normal test with no skeletal disease (d). From these data four ratios can be computed:

True positive ratio (sensitivity) $= a/(a+b)$
False positive ratio $= c/(c+d)$
True negative ratio (specificity) $= d/(c+d)$
False negative ratio $= b/(a+b)$

The sensitivity and specificity of each marker were assessed at a cut-off point corresponding to the limit of the normal range for each biochemical test. However, each of these markers had a range of values in addition to an "abnormal" or "normal" result, and a change in the cut-off point used would affect test specificity and sensitivity. The effect of changes in the cut-off point on test sensitivity and specificity was described using a ROC curve—a plot of true positive against false positive ratios for varying cut-off points (Fig.).

Results

Urinary excretion of calcium and urinary 6-oxo prostaglandin $F_1\alpha$ and serum osteocalcin did not discriminate between patients with benign and those with malignant disease, either with or without metastases. The remaining four markers showed significant differences between patients with and without metastases. However, there were no significant differences in mean values between patients with benign prostatic hyperplasia and those with prostatic carcinoma without metastases,

Table Biochemical values (mean ± SEM) in patients with benign prostatic hyperplasia and prostatic carcinoma without metastases (control patients, n = 30) and in patients with skeletal metastases (n = 72). *P* values refer to the significance of differences between patients with metastases and controls. The relative sensitivity was calculated for each marker using a cut-off point of the upper value of the reference range (lower value in the case of serum albumin). NS = not significant.

Marker	*Control patients*	*Prostatic cancer with metastases*	*P* <	*Relative sensitivity*	*Reference range*
Serum alkaline phosphatase (iu/l)	72.1 ± 3.7	433 ± 57	0.001	80.5%	35-105
Serum acid phosphatase (iu/l)	3.9 ± 0.2	69 ± 13	0.001	80%	<6.4
Urine hdyroxyproline/creatinine	22.6 ± 1.7	66.7 ± 7.8	0.001	68%	<30
Serum albumin (g/l)	40.7 ± 0.5	36.9 ± 0.6	0.001	30%	35-53
Urine 6-oxo-PGF$_1$α/creatinine (pmol/mmol)	72.6 ± 7.3	94.8 ± 16.3	NS	—	<140
Urine calcium/creatinine (nmol/mmol)	0.24 ± 0.03	0.24 ± 0.02	NS	—	<0.3
Serum osteocalcin (ng/ml)	23.9 ± 4.5	27.9 ± 6	NS	—	7-30

and therefore these data were combined to enable comparison between patients with and those without skeletal metastases.

Alkaline phosphatase had the greatest sensitivity calculated by decision matrix analysis using a cut-off point at the upper limit of the reference range (Table). At this point the test also had maximum specificity (no false positive results). ROC curve plots of acid phosphatase, hydroxyproline and albumin at cut-off points that allowed no false positives reduced the sensitivity of each test (71, 43 and 10% respectively), suggesting that the upper limit of the reference range (or lower in the case of albumin) may not be appropriate for confident diagnosis of skeletal metastases using these latter three markers. Indeed the respective cut-off points for maximum specificity of these tests were: acid phosphatase 7.5 iu/l, hydroxyproline 50 mmol/nmol and albumin 30 g/l.

None of the markers conformed to the optimal curve (Fig.), although that of alkaline phosphatase was closest in configuration. The choice of a cut-off point that made each test most sensitive (to detect as many patients with metastases as possible) increased the number of false positive diagnoses—an effect more marked with hydroxyproline and serum albumin than with acid or alkaline phosphatase (Fig.).

Discussion

The value of a diagnostic marker lies in its ability to detect patients with disease (test sensitivity) and to exclude patients without disease (test specificity). Each test has had its proponents but little attempt has been made to assess their relative merits. None of the tests we examined was capable of discriminating between patients with benign prostatic disease and those with carcinoma, but without skeletal metastases. Thus any potential value of these tests in prostatic carcinoma resided solely in their power to distinguish between patients with and those without skeletal metastases. In this respect, determination of alkaline phosphatase activity was marginally better than acid phosphatase and clearly superior to the other tests that we examined. The sensitivity of alkaline phosphatase as a marker of skeletal disease is dependent, nevertheless, upon the choice of an appropriate cut-off point for the test. The upper limit of the normal range is not necessarily the best cut-off, and the selection of an appropriate point is dependent on the use to be made of the test, and the number of false positives and false negatives acceptable in clinical practice (Metz, 1978). Both vary with the cut-off used. For example, since the prevalence of disseminated prostatic cancer in the general population is low, cut-off values of alkaline phosphatase might be chosen towards the left of the ROC curve to keep the number of false positives acceptably low. This is desirable in large-scale screening programmes and in the case of alkaline phosphatase corresponds closely to the upper limit of the normal range (105 iu/l). However, in a urological practice considering only patients with proven prostatic cancer, the prevalence of metastatic disease is high, and a cut-off might be selected which operates towards the right of the ROC curve (*e.g.* 70 iu/l). Such criteria would accept a greater number of false positives in order to keep sensitivity high and false negative findings low, which might be used to select patients for further investigation or treatment (*e.g.* scintigraphy or orchiectomy).

We conclude that none of the tests is sufficiently sensitive for detecting the presence or absence of prostatic carcinoma in the general population.

However, serum activity of alkaline or acid phosphatase is the most sensitive and specific index of skeletal metastases. These might be used most appropriately as screening tests in urological practice, particularly when values lower than the upper end of the reference range are accepted.

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The Authors

G. H. Urwin, MB, FRCS, Wellcome Surgical Research Fellow.
R. C. Percival, MB, FRCS, Lecturer in Surgery, Northern General Hospital, Sheffield.
A. J. P. Yates, MB,ChB, BMedSci, MRCP, Clinical Research Fellow.
M. E. Watson, PhD, MB,ChB, FRCS, Consultant Urologist, Royal Preston Hospital.
M. Couch, BMedSci, Research Fellow.
B. McDonald, BMedSci, Research Fellow.
A. R. W. Forrest, MRCP, MRCPath, MCB, FRSC, Consultant Chemical Pathologist.
J. L. Williams, MB, FRCS, Consultant Urologist.
J. A. Kanis, MD, FRCP, MRCPath, Reader in Human Metabolism and Clinical Biochemistry.

Requests for reprints to: J. A. Kanis, Department of Human Metabolism and Clinical Biochemistry, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX.

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Prognostic Significance of Alkaline and Acid Phosphatase and Skeletal Scintigraphy in Carcinoma of the Prostate

M. V. MERRICK, C. L. DING, G. D. CHISHOLM and R. A. ELTON

Departments of Nuclear Medicine, Surgery/Urology and Medical Computing and Statistics, University of Edinburgh and Western General Hospital, Edinburgh

Summary—The prognostic significance of skeletal scintigraphy has been reassessed in relation to other tests by extended follow-up of 220 patients. Skeletal metastases increased in prevalence with T stage and were associated with shorter survival irrespective of age. Early disease, a normal acid or alkaline phosphatase at presentation and well differentiated tumours were associated with longer survival. Alkaline phosphatase alone accounted for all of the differences in survival.

Scintigraphic change preceded elevation of the prostatic acid phosphatase in 81% of the patients whose initial scintigraphy and prostatic acid phosphatase were normal but who developed evidence of distant metastases on follow-up. The mean interval between scintigraphic conversion and the development of overt symptoms was 5.8 months. Our findings discount the value of skeletal scintigraphy for determining prognosis but do indicate that it is more sensitive than the acid phosphatase in identifying patients before they become symptomatic.

Scintigraphy is indicated as a routine staging procedure in all new patients with carcinoma of prostate. In patients with a normal alkaline phosphatase, a baseline and regular follow-up are needed to identify patients likely soon to develop symptoms. If the alkaline phosphatase is elevated at presentation, scintigraphy is necessary to distinguish benign from malignant causes and to determine the extent of skeletal involvement.

It is well established that, in carcinoma of the prostate, scintigraphy is more sensitive than radiology for the detection of skeletal metastases (Buck *et al.*, 1975; Shafer and Reinke, 1977; O'Donoghue *et al.*, 1978; Stone *et al.*, 1980). For this reason, and because it is thought to give some information concerning prognosis (Lund *et al.*, 1984), scintigraphy is widely accepted as an integral part of the staging procedure which precedes definitive treatment of newly diagnosed patients. It has also been used to evaluate the response to treatment during follow-up (Fitzpatrick *et al.*, 1978; Huben and Schellhammer, 1982).

We have undertaken prospectively an extended follow-up of a large group of patients with carcinoma of the prostate, in order to determine the prognostic significance of an abnormal skeletal scintigram in relation to other markers of tumour activity, especially the prostatic acid phosphatase level, serum alkaline phosphatase, symptoms, tumour stage and histological differentiation. The role of skeletal scintigraphy is re-evaluated in the light of our findings.

Patients and Methods

The case records of 282 patients attending the Prostate Clinic at the Western General Hospital, who had been entered serially into the study, were reviewed. All had undergone skeletal scintigraphy

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

on at least one occasion. Clinical and biochemical assessments were carried out at 3-monthly intervals, skeletal scintigraphy and chest X-rays 6-monthly. Clinical evaluation included recording of performance status, body weight, local and systemic symptoms related to the disease (especially bone pain), and a physical examination. Biochemical assessment included a full blood count, serum prostatic acid phosphatase, alkaline phosphatase, urea and electrolytes.

Criteria for inclusion were that patients should have received no systemic treatment before their first skeletal scintigram, had no second malignancy and a histologically proven diagnosis. Two hundred and twenty of the 282 patients reviewed were suitable for inclusion. Thirty were excluded because the diagnosis had not been confirmed histologically, a further 28 because they had received hormone therapy before the first scintigram, and four because of the presence of a proven second malignancy at the time of diagnosis. Scintigraphy was performed not less than 2 h and up to 6 h after intravenous administration of 750 MBq (20 mCi) ^{99m}Tc MDP. The entire skeleton was examined using a Cleon Multidetector Scanner to obtain images of high resolution and high count density (Merrick 1973, 1984). Examinations were interpreted and reviewed by one experienced observer in conjunction with recent radiographs of any scintigraphically suspect region. A significant abnormality was recorded only if there was radiographic confirmation of metastatic involvement or if there was a definite scintigraphic abnormality for which the radiographs provided no benign explanation (such as osteoarthritis or Paget's disease).

Chi-squared tests and multiple logistic regression were used to establish the relationship of the scintigraphic findings to other prognostic factors at presentation. The prognostic significance of individual factors was tested by the Lee-Desu test, and that of all factors together by Cox proportional hazards regression.

Results

Forty-two per cent of the patients had scintigraphic evidence of skeletal metastases at presentation. Full clinical staging was available in 207. Discounting a statistically non-significant anomaly resulting from the very small number of patients with T1 disease, the prevalence of skeletal metastases increased significantly with T stage ($P<0.001$) (Table 1).

Table 1 Relationship of Scintigraphic Findings to T stage

T stage	*0*	*1*	*2*	*3*	*4*
No deposits (percent)	38 (86.4)	4 (57.1)	26 (63.4)	47 (51.4)	5 (21.7)
Deposits (percent)	6 (13.6)	3 (42.9)	15 (36.6)	45 (48.9)	18 (78.3)

$\chi^2=29.2$ $P<0.001$.

Table 2 Relationship of Scintigraphic Findings to Serum Phosphatase Levels

Plasma acid phosphatase *Plasma alkaline phosphatase*	*Normal* *Normal*	*Raised* *Normal*	*Normal* *Raised*	*Raised* *Raised*
No bone metastases	78	22	4	2
Bone metastases	17	21	8	30
(percentage abnormal)	(18)	(49)	(67)	(94)

The relationship between the findings on skeletal scintigraphy at presentation and measurements of plasma alkaline and acid phosphatase at that time are shown in Table 2 for the 165 patients in whom this data was available. Evaluation of either the acid or the alkaline phosphatase contributed independently to the increased probability of skeletal metastases. This was confirmed by a multiple logistic regression: plasma alkaline phosphatase and plasma acid phosphatase each significantly influenced the chance of metastases for any given level of the other ($P<0.001$ in both cases). There was no significant difference in age between patients with and those without skeletal metastases (Wilcoxon Rank Sum Test). There was an inverse relationship (Table 3) between the degree of differentiation and the incidence of skeletal metastases ($P<0.05$).

Survival curves were calculated for the entire group and for a number of subgroups. Irrespective of age, survival was significantly worse in patients with skeletal metastases (Figs 1 and 2) ($P<0.001$;

Table 3 Relationship between Scintigraphic Findings and Tumour Differentiation

Differentiation	*Well*	*Moderate*	*Poor*
No metastases (percent)	57 (68.7)	28 (53.8)	13 (43.3)
Metastases (percent)	26 (31.3)	24 (46.2)	17 (56.7)

$\chi^2=6.8$ $P<0.05$.

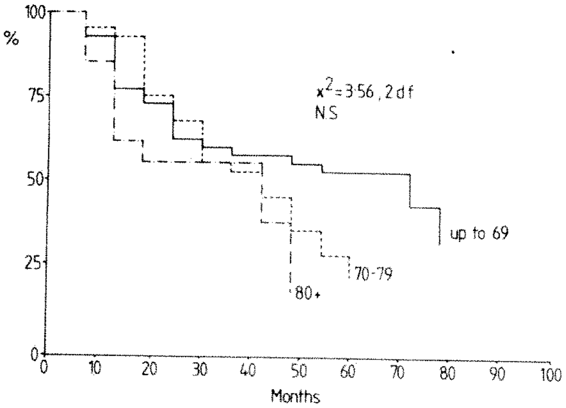

Fig. 1 Survival by age at presentation.

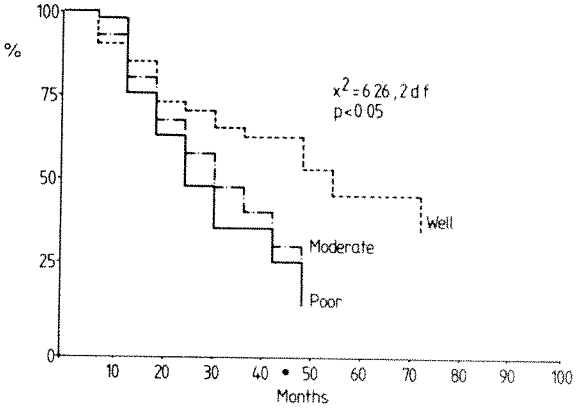

Fig. 4 Survival by histological grading.

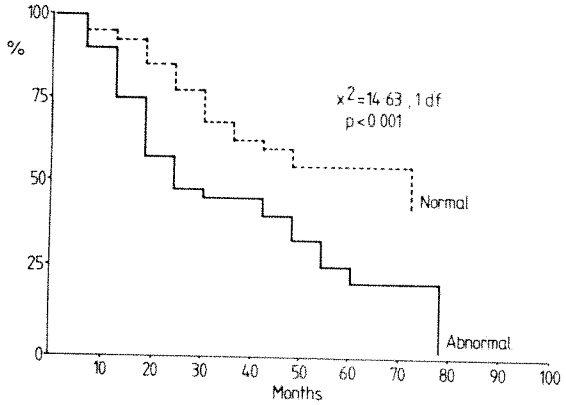

Fig. 2 Survival by scintigraphic findings.

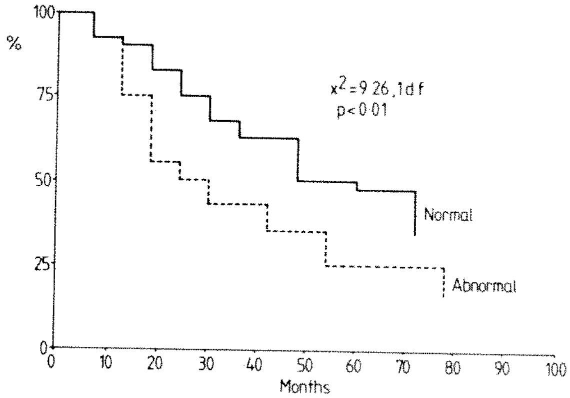

Fig. 5 Survival by plasma acid phosphatase.

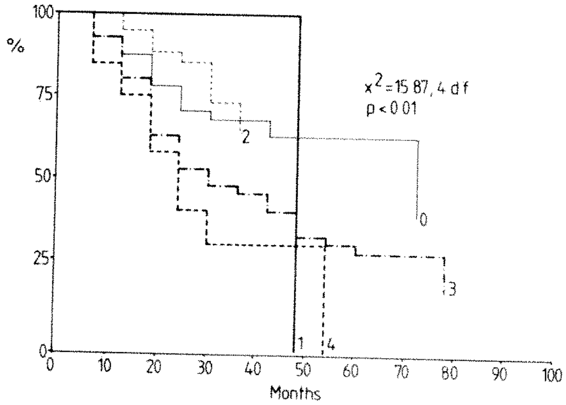

Fig. 3 Survival by T stage.

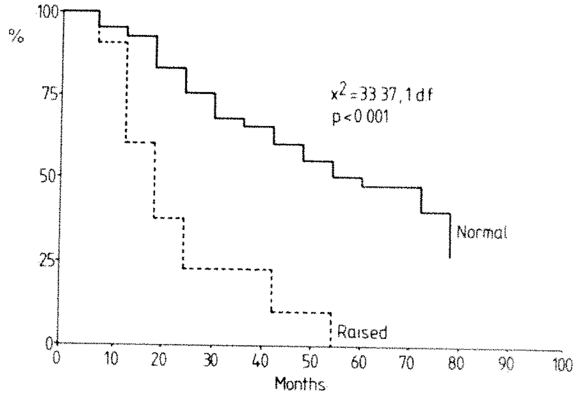

Fig. 6 Survival by plasma alkaline phosphatase.

Lee-Desu test). Patients with stages 0 to 2 disease had a longer survival than those in stages 3 or 4 ($P<0.01$) (Fig. 3), and patients with well differentiated tumours survived longer than those with poorly differentiated ones ($P<0.05$) (Fig. 4).

The survival of patients with a raised acid phosphatase at presentation was significantly shorter than that of those with normal values (Fig. 5) ($P<0.01$). The difference was much greater when considering alkaline phosphatase (Fig. 6) ($P<0.001$). However, the survival of patients with a normal alkaline phosphatase but with skeletal metastases was no worse than that of those without evidence of skeletal metastases. Multivariate analysis using the Cox proportional hazards test showed that the alkaline phosphatase alone accounted for all of the differences in survival. None of the other factors, including the bone scan, was significant, given the alkaline phosphatase findings (Fig. 7). Scintigraphy gave no additional information about prognosis in patients with a normal alkaline phosphatase.

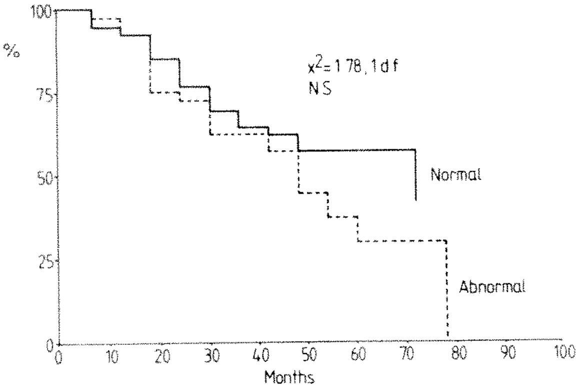

Fig. 7 Survival by scintigraphic findings in patients with normal plasma alkaline phosphatase.

Twenty-one patients with normal bone scintigraphy and normal acid phosphatase levels at the time of diagnosis who were not receiving systemic therapy subsequently developed abnormal skeletal scintigrams. Eleven (52%) had normal and six (29%) elevated prostatic acid phosphatase levels when the scintigraphic change occurred. In only four did the prostatic acid phosphatase rise precede the scintigraphic change.

Forty-nine (55.7%) of the 87 patients with abnormal scintigrams at presentation had disease-related skeletal pain at that time. Fifteen who had evidence of metastases at presentation but had no skeletal symptoms were given deferred therapy. Thirteen of them developed symptoms between 1 and 12 months after the scintigraphic findings, the mean interval being 5.8 months. One died 4 months after presentation without skeletal symptoms and the other was given diethyl stilboestrol 5 years later because of local progression of disease but remained otherwise asymptomatic.

Sixty-eight of the patients with normal scintigraphic findings initially had early local disease and 52 locally advanced disease. The rate at which skeletal metastases developed is shown in Figure 8. The mean interval required for conversion from normal to abnormal scintigraphic findings in patients with early local disease was 26.4 months, and in the more advanced group 17.3 months.

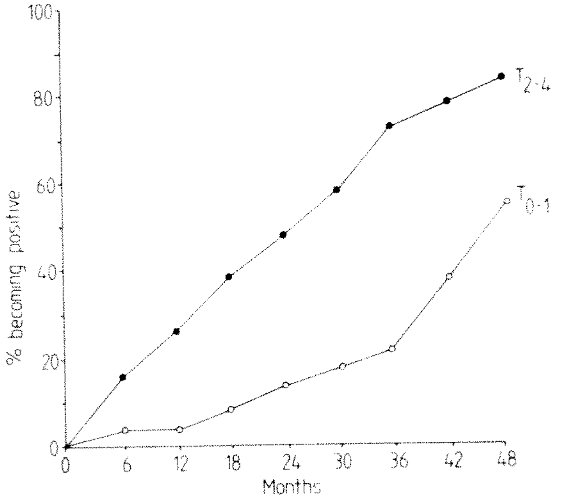

Fig. 8 Interval to first evidence of skeletal metastases in patients with normal staging scintigrams by T stage.

Discussion

It is widely agreed that skeletal scintigraphy is an essential part of the staging procedure in patients presenting with carcinoma of the prostate. Opinions differ regarding the use of routine skeletal scintigraphy for follow-up of these patients. Huben *et al.* (1982) concluded that the low incidence of patients in whom a scintigraphic abnormality was the only evidence of progression did not support its routine use after definitive therapy for localised carcinoma of the prostate. In their series they did not find any patient with a scintigraphic abnormality in the absence of either bone pain or an elevated serum acid phosphatase, and therefore suggested that routine scintigraphic follow-up of such patients is neither medically productive nor cost-effective. On the other hand, Fitzpatrick *et al.* (1978) observed that 74% of patients whose scintigraphic appearance changed from normal to abnormal had a normal acid phosphatase and 84% were asymptomatic when the change occurred.

In the present series, elevation of prostatic acid phosphatase preceded the scintigraphic change in only 19% of patients whose scintigraphy and prostatic acid phosphatase were initially both normal. The mean interval between scintigraphic conversion and the development of overt symptoms was 5.8 months, suggesting that there may be a role for regular scintigraphic follow-up of patients who are asymptomatic and have normal staging scintigraphy. The prevalence of scintigraphic abnormalities at the time of diagnosis, and their relationship to tumour staging, is comparable with those previously reported by O'Donoghue *et al.* (1978) and Bisson *et al.* (1974). It is not surprising that the probability of skeletal metastases is higher in patients with locally advanced disease than in those with early local disease. In a previous series of patients from this clinic (Stone *et al.*, 1980) we were unable to show any correlation between the scintigraphic results and the degree of histological differentiation. However, the present larger series, which includes the cases previously reported, has confirmed that scintigraphic abnormalities are commoner in the more undifferentiated tumours.

We have made no attempt in this study to numerate the extent of abnormality or the degree of change on consecutive examinations. The scintigraphic appearances are only indirectly related to tumour activity, as they are an indicator of the osteoblastic response of the normal bone cells to tumour-induced osteoclasis, rather than a direct reflection of activity in the tumour itself. Despite optimistic reports by other workers, we feel that the relationship is too indirect to be of any value. The significance of a persistent scintigraphic abnormality in a treated patient who is clinically asymptomatic and whose biochemical markers have reverted to normal is unclear.

Lund *et al.* (1984), reporting on EORTC protocol No. 30762, concluded that skeletal scintigraphy at diagnosis is of prognostic value, as those with scintigraphic abnormalities have a shorter survival. Although this is confirmed in our study, we have also shown that a raised plasma alkaline phosphatase is a more important prognosticator of survival than scintigraphy and that the entire difference between those with and those without scintigraphic abnormalities can be explained by the raised plasma alkaline phosphatase. This should not be surprising. Survival is *a priori* more likely to be related to the existence of metastases than to their site and alkaline phosphatase is not specific to the skeleton, or to the presence of metastases. Indeed the skeleton may well be one of the less lethal sites for metastases to occur.

Our findings therefore raise serious doubts about the justification for using skeletal scintigraphy in order to determine prognosis. It is clear from our results that skeletal scintigraphy gives no additional prognostic information regarding survival beyond that obtained by measurement of the plasma alkaline phosphatase. However, this does not mean we consider that skeletal scintigraphy should no longer be performed. Prediction and prevention of morbidity are at least as important as the prediction of mortality. Alkaline phosphatase cannot distinguish between local and disseminated disease, with their different therapeutic implications. Moreover, the alkaline phosphatase, although very sensitive, is non-specific and cannot differentiate metastases from benign conditions such as Paget's disease, which are common in the same population (Merrick and Merrick, 1985).

Other questions which have not been answered in the present study are whether serial scintigraphy, by identifying patients who are at imminent risk of becoming symptomatic, can alter clinical management and whether the measurement of isoenzymes, which were not available during the greater part of this series, has any advantage over the older techniques of measurement of total alkaline phosphatase. As it appears that it is the existence of metastases rather than their location which affects survival, the less specific technique might prove the more sensitive.

It is thus evident that the reasons for performing skeletal scintigraphy as a routine staging procedure in all patients with carcinoma of the prostate have changed. If the alkaline phosphatase is raised, scintigraphy is necessary to direct radiology to the appropriate sites, for differential diagnosis between metastases and the various benign causes, and to distinguish local from disseminated disease, in order to determine the appropriate treatment. In patients with a normal alkaline phosphatase it is required as a baseline to identify on follow-up those who are likely shortly to develop symptoms. In neither group is its purpose to indicate the probable duration of survival.

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Generalised Increase in Bone Resorption in Carcinoma of the Prostate

G. H. URWIN, R. C. PERCIVAL, S. HARRIS, M. N. C. BENETON, J. L. WILLIAMS and J. A. KANIS

University Departments of Human Metabolism and Clinical Biochemistry, and Pathology, University of Sheffield; Department of Urology, Royal Hallamshire Hospital, Sheffield

Summary—Several indirect biochemical indices of bone resorption are increased in patients with carcinoma of the prostate and skeletal metastases. We have examined histological indices of bone resorption in biopsies from affected patients. Bone-forming surfaces and active osteoblast numbers were increased in skeletal sites adjacent to tumour tissue and indices of bone resorption were significantly increased at sites adjacent to tumour. Contrary to expectation, indices of bone resorption were also increased in bone distant from skeletal metastases. These findings suggest that prostatic cancer induces generalised loss of trabecular bone which may minimise disturbances in plasma calcium homeostasis but could contribute to morbidity.

Osteosclerotic metastases are characteristic of prostatic carcinoma. The increase in bone mass adjacent to tumour tissue is associated with increased numbers of active-looking osteoblasts (Jacobs, 1983), which may be due to the local synthesis of humoral factors by tumour cells (Jacobs *et al.*, 1979). The possibility that bone resorption may also be increased has been relatively neglected. This is surprising, since urinary hydroxyproline excretion is high in patients with disseminated skeletal metastases and, indeed, may be used as a marker to follow the progression of the disorder. It has usually been assumed, however, that the source of urinary hydroxyproline is from collagen turnover of tumour tissue. A number of observations suggest that a component of the total excretion of hydroxyproline may be derived from the collagen breakdown of bone. Thus the urinary excretion rate of hydroxyproline correlates closely with serum activity of alkaline phosphatase, and the administration of inhibitors of bone resorption, such as calcitonin or diphosphonates, acutely decreases hydroxyprolinuria (Urwin *et al.*, 1984). In order to explore this notion directly we measured several histological indices of bone resorption in bone biopsies taken from patients with skeletal metastases.

Patients and Methods

Trans-iliac bone biopsies were taken from 19 patients with prostatic carcinoma and scintigraphic evidence of skeletal metastases using a Meunier (7.5 mm internal diameter) trephine under local anaesthesia. Biopsy specimens were fixed in 5% buffered formalin at pH 7.4 and embedded in methylmethacrylate (British Drug Houses Chemicals, Ltd). Consecutive 7 μ sections were cut with a Jung-K microtome and stained with Goldner's trichrome. The following measurements were made on trabecular bone using techniques previously described (Kanis *et al.*, 1979).

Bone matrix area: the percentage of sectional area occupied by mineralised and non-mineralised bone matrix.

Osteoblast surface: the percentage of total trabecular surface occupied by plump active-looking osteoblasts.

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Rough crenated surface: the fully mineralised trabecular surface with a scalloped surface transecting mineralised bone lamellae, expressed as a proportion of the total trabecular surface.

Active resorption surface: the fully mineralised surface occupied by multinucleated giant cells (osteoclasts) and mononuclear cells closely apposed to the bone surface, expressed as a percentage of the total trabecular surface. The active resorption surface was not measured in biopsies with tumour infiltration since the presence of tumour cells impaired confident identification of mononuclear osteoclasts.

The significance of differences between mean values was computed using Student's t test (two tailed) for unpaired samples.

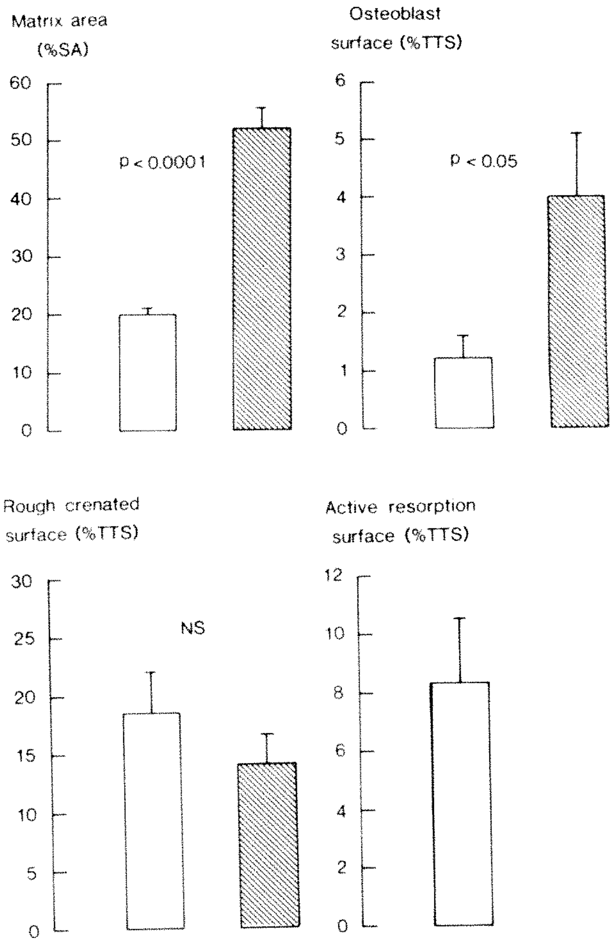

Fig. Morphometric measurements in trabecular bone in patients with carcinoma of the prostate and skeletal metastases. Mean values (±SEM) are shown for biopsies free of tumour (open bars) and those with metastatic infiltration (hatched bars). P values refer to the significance of differences between measurements from involved and uninvolved bone. NS = not significant.

Results and Discussion

Eleven of the 19 biopsy specimens were infiltrated by tumour tissue and 8 were not. In bone infiltrated by tumour tissue there was a marked and significant increase in the mineralised matrix area and osteoblast surface consistent with augmented rates of bone formation (Fig.). Bone resorption as judged by the rough crenated surface (normal range 2-4%) was increased in both involved and tumour-free bone, but more markedly in the latter. The active resorption surface was also increased in uninvolved bone (NR < 1%) but was not examined in biopsies with tumour invasion (Fig.).

The finding of osteosclerosis at sites of tumour deposition is not surprising, and the increased numbers of osteoblasts found in our patients as well as in other studies (Jacobs *et al.*, 1979; Jacobs and Lawson, 1980) support the notion that local increases in bone formation are principally, if not exclusively, due to the activation of normal bone cells by tumour tissue. Osteoblast numbers were not increased at sites unaffected by tumour tissue, suggesting that local humoral factors mediate this effect.

Our findings suggest that bone resorption is also increased, particularly at sites distant from tumour metastases as judged by the increase in the rough crenated and the active resorption surface. It should be noted that neither measurement indicates the rate of bone resorption, but only the surface of the bone undergoing or having undergone resorption in the past (Baron *et al.*, 1980). Nevertheless, the active rather than the total resorption surface correlates closely with biochemical indices of bone resorption in generalised metabolic bone disease (Cundy *et al.*, 1983). Our previous observations that high urinary excretion rates of hydroxyproline in prostatic carcinoma can be decreased by the administration of specific inhibitors of bone resorption (Percival *et al.*, 1985), support the histological findings and suggest that resorption rates were increased in trabecular bone.

Increased bone resorption at sites distant from tumour metastases suggests that it is mediated by factors other than those which stimulate osteoblast activity at sites of tumour deposition. It is possible that such factors might be secreted by tumour tissue itself, and conditioned medium of human prostatic cell lines (PC3 cells) has been shown to possess bone resorbing activity *in vitro* (Rodan *et* *al.*, 1983). It is also possible that the generalised increase in bone resorption is an adaptation to the positive skeletal balance induced by prostatic tumour. An increased influx of calcium into bone would decrease serum calcium and stimulate the secretion of parathyroid hormone and thus synthesis of calcitriol, the most active metabolite of vitamin D. Both of these hormones increase serum calcium by their actions on target organs. These actions include increased intestinal absorption of calcium, hypophosphataemia and increased bone resorption, which have been described in prostatic carcinoma (Jacobs, 1983). Moreover, we have recently shown high values of calcitriol in affected patients which decrease with effective hormonal treatment (Guilland-Cumming *et al.*, 1983).

Irrespective of the mechanism by which increased bone resorption occurs, bone loss may be increased by hormonal manipulation since gonadal steroids have anabolic effects on bone. Thus procedures such as orchiectomy or the use of LHRH agonists are likely to accelerate bone loss and could contribute to the morbidity of affected patients.

Acknowledgements

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The Authors

G. H. Urwin, FRCS, Wellcome Surgical Research Fellow.
R. C. Percival, FRCS, Lecturer in Surgery, Northern General Hospital, Sheffield.
S. Harris, MB, BCh, Lecturer in Pathology.
M. Beneton, HNC, Research Assistant.
J. L. Williams, FRCS, Consultant Urologist.
J. A. Kanis, MD, FRCP, MRCPath, Reader in Human Metabolism and Clinical Biochemistry.

Requests for reprints to: J. A. Kanis, Department of Human Metabolism and Clinical Biochemistry, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX.

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Is Delayed Treatment Justified in Carcinoma of the Prostate?

M. C. PARKER, A. COOK, P. R. RIDDLE, I. FRYATT, J. O'SULLIVAN and R. J. SHEARER

Department of Urology, St George's and St James's Hospitals, London

Summary—We report a retrospective survey of 263 patients with prostate cancer presenting between 1975 and 1979, with a minimum follow-up period of 5 years. We have evaluated the effects of anti-cancer therapy on survival and disease-free interval. The mean survival time of all patients was 39.6 months.

Of 91 patients (37.7%) with demonstrable bone metastases at presentation, 64 (70.3%) have died of prostatic cancer, the mean duration of survival being 25 months. There was no difference in terms of response to treatment or of duration of symptom-free life between patients treated by immediate hormone manipulation and those in whom treatment was delayed.

Of 115 patients without metastases at presentation, 42 (36.5%) received no anti-cancer treatment. Thirty-seven (32.2%) have died of unrelated causes and 39 (33.9%) are alive and well.

Neither survival nor subjective response to treatment was adversely affected by delaying treatment.

The well-discussed Veterans' Administration studies (VACURG, 1967; Bailar *et al*, 1970) showed that hormone manipulation did not improve survival in advanced prostatic cancer and suggested that treatment should be delayed until required for symptomatic relief. Since then there has been increased emphasis on delayed treatment (Bailar *et al.*, 1970). A prospective trial of immediate versus delayed treatment in patients with advanced local disease or asymptomatic metastatic disease is currently being undertaken by the Medical Research Council.

Delayed treatment allows the clinician to withhold therapy until such time as the patient's symptoms demand relief, but can only be justified if the morbidity of the disease is not increased and if effective palliation of symptoms is unimpaired. We have reviewed all of our patients presenting with prostatic cancer between 1975 and 1979 and report our evaluation of the aspects of management.

Patients and Methods

We have reviewed 263 patients who presented with histologically proven prostatic cancer between 1975 and 1979, so that the minimum follow-up is 5 years.

The nature and duration of symptoms before presentation were recorded. The survival of all patients was determined from the hospital records, as was the disease-free interval (time from diagnosis to first evidence of progression of cancer) and response to treatment both in terms of subjective improvement and length of response until second progression. Definitions of progression and of response to treatment were as laid down by the British Prostate Group, 1982 (unpublished data).

The tumours were assessed and graded histologically according to the TNM classification (UICC, 1978). Where the records did not indicate tumour grade, one of us (J. O'S) conducted a histological review. T category was evaluated by cystourethroscopy and bimanual examination under anaesthesia. Evidence of distant metastases was taken as a positive radioisotope bone scan or radiological ske-

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

letal survey *and* elevated serum acid or alkaline phosphatases.

Lymph node staging by bipedal lymphography was conducted in insufficient numbers for detailed analysis. Lymph node biopsy was not done.

Inevitably in a retrospective series, treatment varied. Patients with obstructive urinary symptoms were treated by transurethral prostatectomy (TUR) and we have not considered this as anti-cancer treatment. Locally invasive non-metastatic tumours were treated by radiotherapy, hormone manipulation or observation.

Patients with asymptomatic metastases were either treated by hormone manipulation or were observed.

Symptomatic metastases were treated by hormone manipulation (in the earlier part of the study stilboestrol, later superseded by orchiectomy).

Patients who progressed after primary anti-cancer treatment were treated by further hormone manipulations (pituitary ablation or aminoglutethimide) and/or palliative radiotherapy.

Statistical analysis was done by applying log rank and log trend tests to the Kaplan Meier life tables.

Results

Two hundred and sixty-three patients presented between 1975 and 1979: 22 were lost to follow-up, leaving 241 for analysis. Of these, 115 (47.7%) were free of metastases (MO) at the time of diagnosis, 91 (37.8%) had proven metastases (M1) and 35 (14.5%) could not be classified (MX). The presenting symptoms and method of diagnosis are shown in the Table.

Thirty-nine tumours (16%) were well differentiated (G1), 118 (41%) moderately differentiated (G2) and 82 (34%) poorly differentiated (G3).

All patients were dead within 11 years, with a 5-year survival rate of 50%; 50% of all patients progressed within 2 years of diagnosis and of those a further 60% progressed again after another 2 years.

Survival of those patients who had anti-cancer therapy compared to no anti-cancer therapy is shown in Figure 1. Figures 2 and 3 show that anti-cancer treatment did not influence the overall time from diagnosis to first progression or from first to second progression.

The relation between survival and histological grade is shown in Figure 4; we saw a similar pattern in time to first progression related to histological grade.

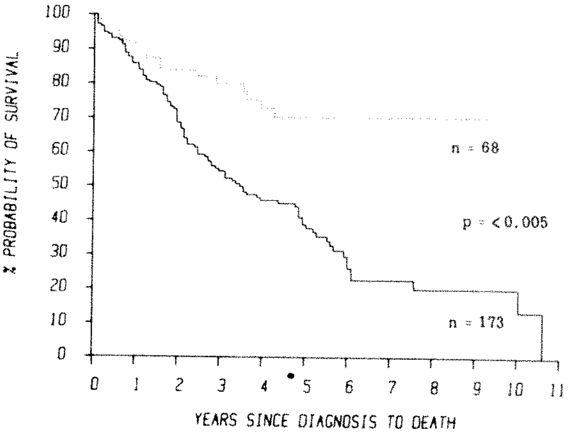

Fig. 1 Anti-cancer Rx *vs* no anti-cancer Rx—all patients' overall survival.

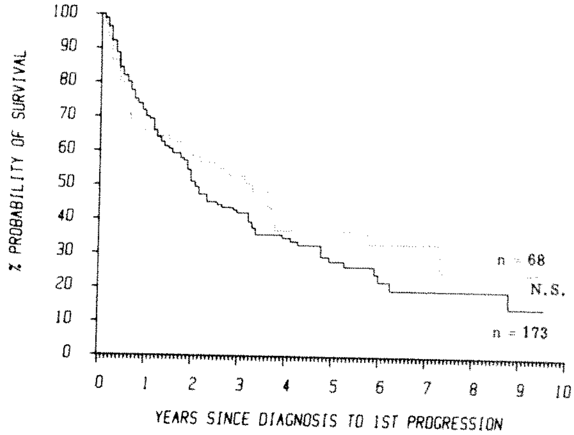

Fig. 2 Anti-cancer Rx *vs* no anti-cancer Rx—all patients' time to first progression.

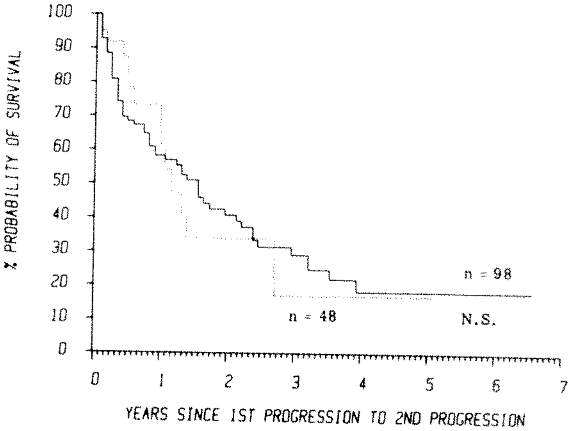

Fig. 3 Anti-cancer Rx *vs* no anti-cancer Rx—all patients' time from first to second progression.

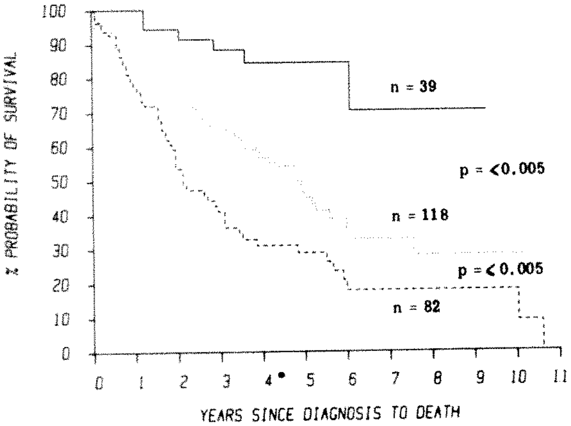

Fig. 4 Survival curves of G1, G2 and G3 tumours.

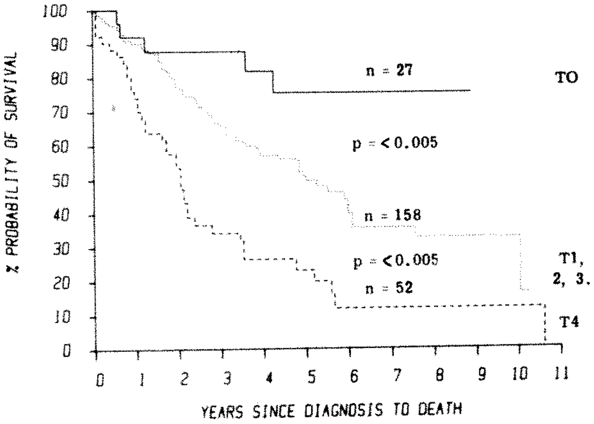

Fig. 7 Survival curves of TO *vs* T1, 2 and 3 *vs* T4 tumours.

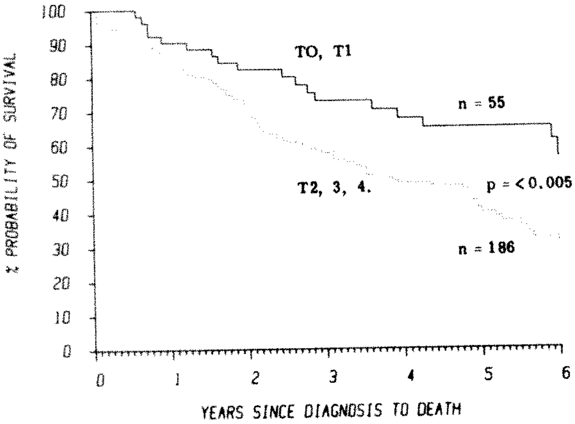

Fig. 5 Survival curves of TO and T1 *vs* T2, 3 and 4 tumours.

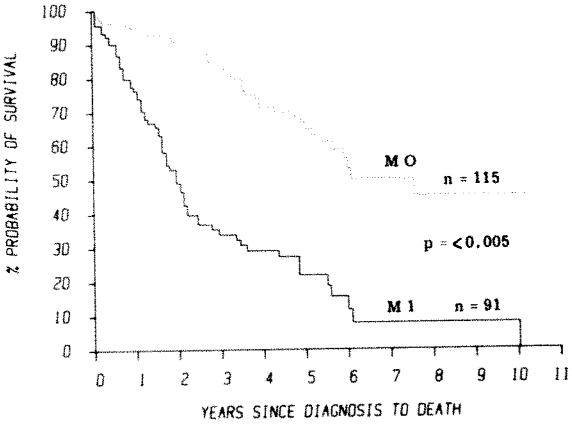

Fig. 8 Survival curves of MO *vs* M1 tumours.

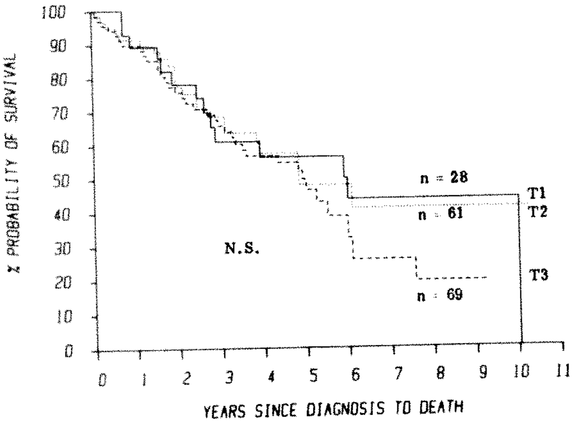

Fig. 6 Survival curves of T1, 2 and 3 tumours.

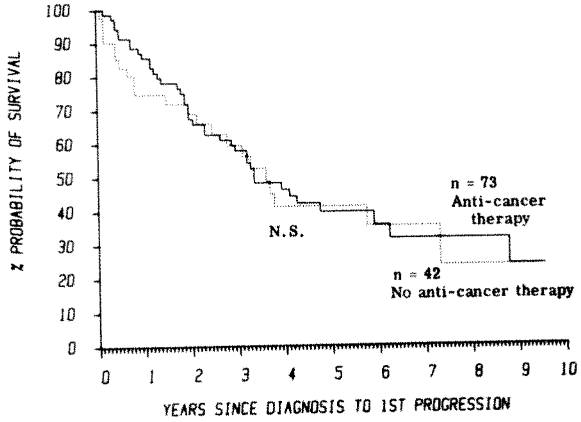

Fig. 9 Time to first progression in MO patients: anti-cancer Rx *vs* no anti-cancer Rx.

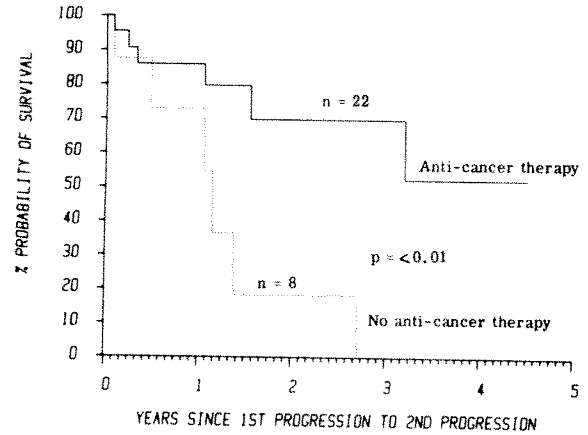

Fig. 10 MO patients who have progressed: anti-cancer *vs* no anti-cancer Rx.

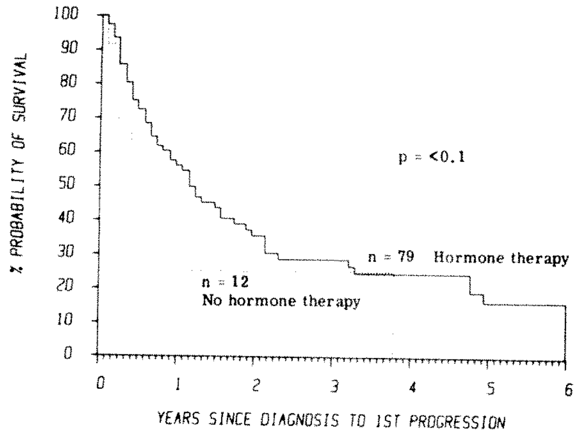

Fig. 11 M1 patients hormone Rx *vs* no hormone Rx: time to first progression.

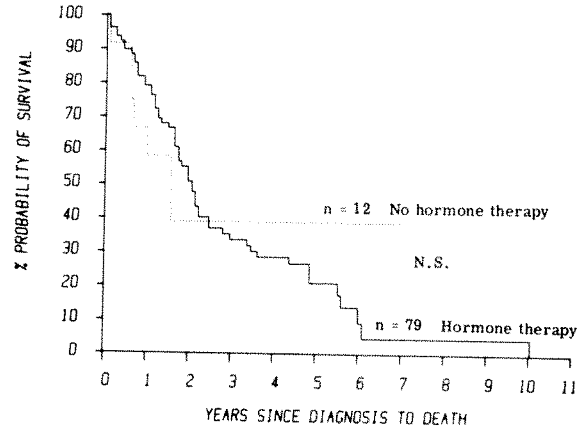

Fig. 12 M1 patients—hormone Rx *vs* no hormone Rx: overall survival.

The survival of patients with TO and T1 compared with T2, 3 and 4 tumours is shown in Figure 5. There is a significant difference in survival but not in time to first progression. This finding prompted us to look more closely at the survival of patients in each T category. Figure 6 shows that there is no difference in survival between T1, 2 and 3 patients; this is also seen in time to first progression. Figure 7 shows the survival of patients with TO and T4 tumours against the combined survival of T1, T2 and T3 patients. This pattern also holds for time to first progression. Figure 8 compares survival of patients free of metastases at presentation (MO) with those with demonstrable metastases (M1). The time to first progression curves are similar. Within the MO group there is no difference in the time to first progression between those patients who had anti-cancer therapy and those who had no anti-cancer therapy (Fig. 9). Figure 10 shows that when these patients do progress locally and are then treated with anti-cancer therapy, they are still able to respond. The numbers are small but all eight patients in this subgroup who did not receive any anti-cancer treatment at first progression were dead within 3 years, whereas 50% of the 22 patients who did receive such treatment were still alive 4 years later.

In patients who presented with demonstrable metastases (M1), hormone manipulation hardly influenced the time to first progression and did not influence overall survival (Figs 11 and 12).

Table Presenting Symptoms and Methods of Diagnosis

Presenting symptoms	*n = 241*	
Retention	*n* = 96 (39.8%)	acute n = 65 (67.7%) chronic = 31 (32.3%)
Prostatism	n = 160 (66.4%)	
Haematuria	n = 23 (9.5%)	
Other urinary	n = 9 (3.7%)	
Bone pain	n = 33 (13.7%)	
Method of diagnosis		
T.U.R.	n = 159 (65.9%)	
T.P.B.	n = 18 (7.5%)	
T.R.B.	n = 49 (20.3%)	
Franzen	n = 15 (6.3%)	

Discussion

Hormone manipulation has been the basis of management of prostatic cancer for 45 years (Huggins and Hodges, 1941). However, studies of the natural history of the disease have shown that in many instances cancer progression does not occur within the lifetime of the patient. The recognised morbidity and mortality of oestrogen administration and the psychological trauma of orchiectomy have prompted many to advocate expectant treatment for asymptomatic patients (Bailar *et al.*, 1970). It is also widely accepted that hormone manipulations do not prolong life in metastatic patients (VACURG, 1967).

More recent studies have suggested that even in early disease, treatment does not influence prognosis (Byar, 1980).

It has been our philosophy that in patients of the age range of those with prostatic cancer, survival is not the only or the best means of assessing the success or failure of a particular management regime. Of greater importance is the quality of life. The first potential danger of delay in initiating therapy is that patients who do not have metastases and are therefore possibly curable will subsequently develop either locally incurable or metastatic disease. Our observation that over a third of patients without metastases at presentation needed no treatment before death or within 5 years of diagnosis indicates that that fear is groundless. Withholding therapy in these patients neither reduces longevity nor impairs the subsequent response to treatment. There is some indication that treatment of localised disease reduces the risk of local progression, which is often the most distressing aspect of prostatic cancer. However, with this proviso it is clear that delay in initiating treatment does not materially affect the outcome for the worse. The second potential danger of delayed treatment is that subsequent response to anti-cancer therapy is less effective. We have found that when previously untreated patients have progressed (usually with metastases) the response to treatment has been in accordance with expectation (80-85% subjective response) and that the duration of response is similar to treated asymptomatic patients.

There is a definite need for a properly controlled prospective trial of delayed treatment, such as the current MRC Trial, though we are concerned that the protocol of this trial allows both MO and M1 disease to be admitted. Our findings show such a clear difference between these groups that we fear that the MRC study may not provide an indication of the role and place of expectant therapy.

We were also interested to find that T1 tumours behave in all respects as invasive cancer with a prognosis as bad as that of T2 and T3. It is only the true TO tumour with one or two foci of cancer in an otherwise benign gland that behaves in a non-malignant fashion.

It is concluded that delayed treatment is justified in prostatic cancer and that tumour grade and stage have a greater effect on prognosis than treatment. Subjective response to hormone manipulation is not affected by delay and 36% of MO patients will need no anti-cancer therapy within 5 years.

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The Authors

A. Cook, FRCS, Senior Registrar, St George's Hospital.
I. Fryatt, Programmer Statistician, Computer Department, Royal Marsden Hospital, London.
J. O'Sullivan MRCPath, Consultant Pathologist, St George's Hospital.
M. C. Parker, FRCS, Senior Registrar, St George's Hospital.
P. R. Riddle, MS, FRCS, Honorary Consultant, St George's Hospital.
R. J. Shearer, FRCS, Consultant Urologist, St George's Hospital.

Requests for reprints to: R. J. Shearer, Department of Urology, St James' Hospital, Sarsfeld Road, London SW12 8HW.

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Prediction of Response to Radiotherapy for Localised Prostatic Cancer

A. W. S. RITCHIE, G. SMITH, C. PRESTON, L. L. BEYNON, W. DUNCAN and G. D. CHISHOLM

University Departments of Surgery/Urology and Radiation Oncology, Western General Hospital, Edinburgh

Summary—Fifty-one patients with TO-4 NX MO carcinoma of the prostate were treated by external beam radiotherapy. Comparison with 40 patients with TO-3 NX MO disease, whose treatment was deferred initially, showed a higher incidence of local progression in the untreated patients.

Age at presentation and initial T category did not have a significant influence upon the probability of disease progression after radiotherapy, whereas all but one of the irradiated patients with Gleason sum scores ⩾6 progressed.

Treatment-related morbidity was appreciable and prolonged proctitis occurred in 31 patients. There was one treatment-related death. Biopsy 1 year after treatment did not yield information of prognostic significance.

It is recommended that the selection of patients with localised carcinoma of the prostate for treatment by radiotherapy is based on histological grade. The Gleason score is a practical method for identifying those who would best be treated by other methods.

The preferred treatment for localised carcinoma of the prostate is either radical surgery, radiotherapy, hormonal therapy or a combination of these treatments, depending upon the enthusiasm of the advocate (Bagshaw, 1985; Walsh, 1980; Mukamel *et al.*, 1983).

Radical radiotherapy has survival rates comparable to those of radical surgery and has the advantage of avoiding major surgery in an elderly population (Perez, 1983). The adverse effects of radical radiotherapy to the pelvis have been thought acceptable in view of the beneficial effects (Bloom, 1981).

The purpose of this study was an analysis of a group of 51 patients with MO disease. Disease progression was used as the end point for assessment of therapeutic outcome.

Patients and Methods

Fifty-one patients with a mean age 69.5 years (range 51-80) were included in this study (Table 1). The patients were previously untreated, had normal performance status and histological confirmation of the diagnosis of carcinoma of the prostate. Staging included examination under anaesthesia, chest X-ray, bone scintiscan, serum alkaline and acid phosphatase. The grade by Gleason score was recorded on all tissue samples (TUR specimens in all but five patients) and reviewed by one pathologist. The study was not randomised but a contemporary group of 40 patients with T0-3 NX MO disease, who had been selected for deferred treatment, was used for comparison.

Table 1 Details of Patients

	Radiotherapy	*Deferred*
No.	51	40
Mean age	69.5	75.3
T category 0/1	12	24
2	20	8
3	17	8
4	2	—
Mean follow-up (months)	44.6	25.8

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External beam radiotherapy was administered using a small field technique. The fields were localised to the prostate and did not include the common iliac nodes. The internal and external iliac nodes received 50% of the dose to the prostate. Forty-eight patients received megavoltage photon therapy, the target absorbed dose being 55 Gray (modal dose 52.5 Gray) in 20 fractions over 26 to 28 days. Three patients received neutron therapy.

Follow-up was at 3-monthly intervals, when history, examination findings and biochemistry were reassessed. Bone scintiscans and chest X-ray were performed at 6-monthly intervals.

Treatment morbidity was assessed independently using the EORTC/RTOG acute and late morbidity criteria.

Tru-cut needle biopsies of the prostatic remnant were taken from 40 patients at a minimum of 1 year after therapy.

Disease progression was defined as (1) a consistent increase in the T category over two follow-up visits, (2) development of metastases or (3) persistent elevation of serum acid or alkaline phosphatase which could not be explained by other pathology.

Analyses of estimated probabilities of disease progression were performed by life-table and logrank analysis (Peto *et al.*, 1977).

Results

Thirty of the 51 patients (59%) remained alive at the end of the study, with a mean follow-up of 44.6 months (range 19-78). Twenty-two patients (43%) had no evidence of disease progression and of these 18 (82%) were alive. By contrast, 29 patients had evidence of progression and of these 12 (41%) were alive. Local tumour progression was observed in 14. Seventeen patients developed bone metastases and 23 had persistent biochemical changes that suggested extra-prostatic progression. Only two patients showed progression on the evidence of biochemical changes alone.

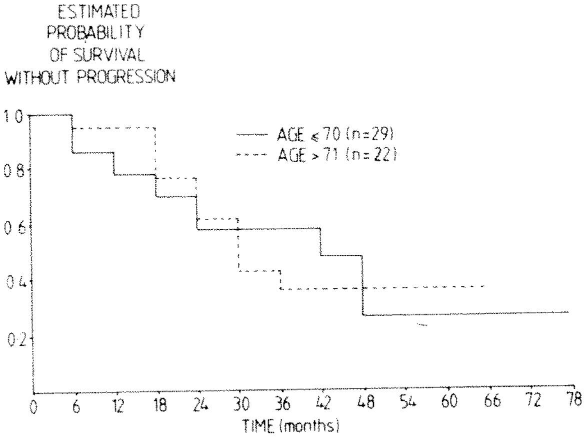

Fig. 1 Life table analysis of the estimated probability of survival without progression by age ($\chi^2 = 0.005$, df = 1 NS).

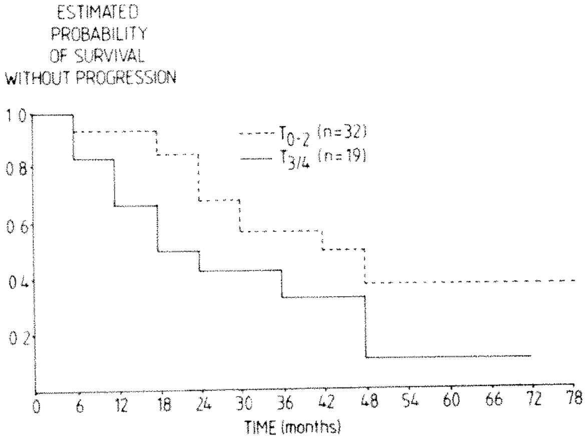

Fig. 2 Life table analysis of the estimated probability of survival without progression by T category at presentation ($\chi^2 = 3.56$, df = 1 NS).

The estimated probability of survival without progression was not related to age at presentation when those aged 70 years or less were compared with the older group ($\chi^2 = 0.005$, df = 1 NS) (Fig. 1). Patients with T category 0-2 at presentation had a lower probability of progression when compared with those with locally advanced tumours (T3 and 4) (Fig. 2) but this difference was not statistically significant ($\chi^2 = 3.56$, df = 1 NS). Patients with a Gleason sum score $\geqslant 6$ had a significantly higher probability of progression when compared with those of sum score 2-5 ($\chi^2 = 18.81$, df = 1, $P = < 0.001$) (Fig. 3). Table 2 compares these two groups of irradiated patients, as defined by the Gleason sum scores, with the untreated patients and gives the number and proportion of patients developing local and distant progression in each group.

Table 3 sets out the treatment-related morbidity. Acute radiation morbidity is that from day 1 to 90 and late morbidity is assessed after day 90. Four patients developed strictures of the posterior urethra, two of which were thought to be the direct result of radiotherapy. One patient developed an entero-cutaneous fistula after a colostomy for bowel obstruction followed by urinary diversion for a "frozen pelvis". His death was considered a direct consequence of the radiotherapy.

Forty patients had a biopsy at least 1 year after therapy. Adequate material for histological analysis was obtained in 31. Histology showed residual tumour in five patients, three of whom subsequently had evidence of disease progression. Cellular abnormalities were noted in a further nine patients, five of whom developed progression (local in 3). Normal prostatic tissue was found in biopsies from 17 patients but follow-up showed disease progression in eight (local in 3).

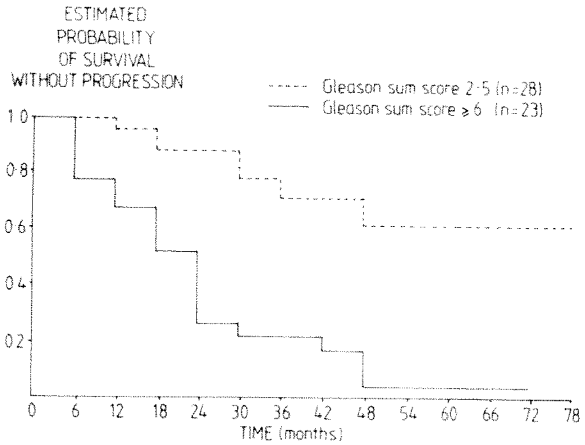

Fig. 3 Life table analysis of the estimated probability of survival without progression by Gleason sum score ($\chi^2 = 18.81$, df = 1, $P = <0.001$).

Table 2 Comparison of Modes and Rates of Disease Progression in Untreated Patients and those Treated by Radiotherapy

		Radiotherapy	
	Deferred	*Sum score 2-5*	*Sum score ≥6*
No.	40	28	23
No. with local progression (%)	22 (55)	6 (21.4)	8 (34.8)
No. developing metastases (%)	7(17.5)	2 (7.1)	15 (65.2)
Any progression (%)	28 (70)	7 (25)	22 (95.6)

Table 3 Treatment-related Morbidity

	Grade	*Acute*	*Late*
Lower GI tract	1*	12	24
	2	24	5
	3	8	1
	4	—	1
Upper GI tract	1	8	—
GU tract	1	18	1
	2	—	5
	3	2	2
	4	—	1
Skin	1	17	6
	2	4	1

* Numbers refer to the grade of toxicity.
0 = No change over baseline.
1 = Mild symptoms not requiring therapy.
2 = Symptoms requiring medical treatment.
3 = Severe symptoms requiring parenteral support.
4 = Complications such as bleeding, perforation or fistula.
5 = Treatment-related death.

Discussion

This study was not a controlled trial. The deferred treatment group was subject to selection on the basis of greater age, poorer performance status, earlier T category (Table 1) and better differentiated tumours. However, it was considered of value to include a contemporary group for comparison of the natural history of the disease with those treated by radiotherapy. The higher local progression rate in the patients who had deferred treatment suggests that radiotherapy does significantly control many of the primary tumours. This study has shown that the pre-treatment Gleason score can identify a population of patients for whom radical radiotherapy alone may not be advised. Patients with Gleason sum scores ≥6 had a significantly higher probability of progression and 65% developed metastases.

Failure to prevent progression in these patients most likely reflects inadequate staging in terms of the status of the lymph nodes (Perez, 1983). Also, the radiotherapy given to these patients did not encompass all of the pelvic lymph nodes. However, Neglia *et al.* (1977), in a randomised study, reported similar survival rates for patients treated with fields that encompassed the prostate alone and for patients who had treatment of the pelvic nodes. McGowan (1981), on the other hand, has suggested that survival may be better if the nodes are included.

We consider that the solution of increasing the field size or total dose must be considered in the light of the risk of increasing the already appreciable treatment morbidity, a factor that has often received scant attention (Paulson *et al.*, 1982; Perez, 1983; Bagshaw, 1985).

An alternative to increasing the field size and/or total dose of radiation may be to give adjuvant hormonal therapy to those with poorly differentiated tumours. Favourable results have been reported using this approach (Mukamel *et al.*, 1983).

Biopsy of the prostatic remnant 1 year after therapy does not, from the evidence of this study, yield information of prognostic value. Our findings agree with previous reports (Abadir *et al.*, 1983; Cox and Kline, 1983) and underline the need for better objective methods for assessment of therapeutic efficiency.

We have chosen to analyse the results in terms of time to first evidence of disease progression rather than overall survival. Reasons for this approach include the age of the patients under study (mean age 69.5 years), the possible influence of second-line treatment on survival and the difficulty in obtaining reliable information on the cause of death. Using this approach in conjunction with close follow-up and logrank analysis we have shown that response to radiotherapy is not homogeneous. Patients with poorly differentiated tumours, irrespective of age and initial T category, are poorly controlled locally and have a high incidence of development of metastases, indicating a need for alternative therapy.

Acknowledgements

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The Authors

A. W. S. Ritchie, MD, FRCSE, Senior Registrar in Urology.
G. Smith, FRCS(Glas), Registrar in Urology.
C. Preston, BSc, MB, ChB, Registrar in Radiotherapy.
L. L. Beynon, FRCS, formerly Senior Registrar in Urology. Now Consultant Urologist, New Cross Hospital, Wolverhampton.
W. Duncan, FRCR, FRCSE, FRCPE, Professor of Radiotherapy.
G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery/Urology and Honorary Consultant Urologist.

Requests for reprints to: A. W. S. Ritchie, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Cord Compression and Carcinoma of the Prostate: is Laminectomy Justified?

J. W. IACOVOU, J. C. MARKS, P. H. ABRAMS, J. C. GINGELL and A. J. BALL

Department of Urology, Southmead Hospital and Department of Neurosurgery, Frenchay Hospital, Bristol

Summary—Metastatic carcinoma of the prostate is a common cause of spinal cord compression. In this review of 37 men who underwent laminectomy for this condition this was the first presentation of previously undiagnosed cancer in 11 (29%).

One year after decompression 17 (50%) were alive. Twenty patients (59%) could walk after laminectomy. All but 8 were relieved of pain and bladder function was improved in 13 (38%). Those ambulant before laminectomy (7) and those with occult prostate cancer did particularly well. Poor results were associated with a rapid onset of paraparesis and pre-operative progression to paraplegia. A delay in diagnosis was detrimental to outcome.

A high index of suspicion in patients with carcinoma of the prostate is essential so that early diagnosis can be made before paraplegia is established. Carcinoma of the prostate must always be excluded in men with cord compression of unknown aetiology.

In the past the commonest malignancy causing spinal cord compression from vertebral metastases was carcinoma of the lung and the prognosis was poor. Recent reports (Livingston and Perrin, 1978; Dunn *et al.*, 1980; Constans *et al.*, 1983) have shown that metastatic carcinoma of the prostate has become a relatively common cause of cord compression and by contrast these patients survive longer and frequently benefit from surgery (Fontana *et al.*, 1980; Stark *et al.*, 1982; Jameson, 1983). However, experiences of poor survival rates and deterioration following laminectomy to relieve cord compression in malignant disease have generated a mood of nihilism amongst surgeons called upon to deal with this problem.

We report a retrospective study of 37 men who underwent laminectomy for spinal cord compression due to metastatic carcinoma of the prostate.

Patients and Methods

The South West Regional Neurological Unit based at Frenchay Hospital in Bristol receives referrals from at least eight District General Hospitals. Those patients who had a laminectomy to relieve spinal cord compression caused by metastatic carcinoma of the prostate during the period July 1978 to July 1983 were reviewed. During this period, 37 men underwent laminectomy; their ages ranged from 52 to 80 years (mean 66.5). In 11 cases (29%) cord compression was the first presentation of previously undiagnosed prostate cancer. Of those with known prostatic disease (26), all but two had symptomatic spinal secondaries and 21 patients had vertebral disease on bone scan. Twenty-one of those with previously diagnosed disease had been treated by hormone manipulation.

The pre-operative history, investigation, subsequent treatment and progress were investigated by reference to hospital notes and contact with the family doctor. The mode and tempo of presentation were considered. The neurological status was classified at presentation to the referring hospital, on admission to and discharge from Frenchay Hospital, and during rehabilitation after transfer back to the District General Hospital. Follow-up was continued until death or 1 January 1985 if still alive.

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Patients were classified as ambulant (with or without mechanical aids) or non-ambulant (paraparetic or paraplegic). Bladder function was classified as normal, symptomatic or requiring a catheter. Pain was the most difficult factor to assess retrospectively, but an attempt was made to classify this as severe, mild, or absent.

A good result was recorded only where functional improvement occurred *i.e.* a non-ambulant patient became ambulant (with or without aids), a catheterised patient could do without a catheter, and where pain was relieved completely, or enough to require only mild analgesia.

Results

The commonest history at presentation was back pain, usually thoracic, with a more recent onset of increasing weakness in the legs together with urinary difficulties (Table 1). The tempo of onset of weakness varied from a few hours to more than 2 weeks.

Table 1 Symptoms and Signs at Presentation (n = 37)

Back pain	34		
Weakness	36	—Ambulant	12
		—Non-ambulant paraparetic	18
		—Non-ambulant paraplegic	6
Bladder function	10	—Normal	
	11	—Difficulty with voiding	
	16	—Retention	

The relevant investigations were serum acid phosphatase, plain X-rays of the spine, isotope bone scan and myelography. Serum acid phosphatase was always raised when carried out at presentation (26 cases). Plain X-rays were reported upon in 31 cases and only one was said to be normal. All others revealed single or multiple abnormalities consistent with bony metastases. Myelography was performed in 24 men and only one patient was found to have an abnormality that did not coincide with that of the plain film. However, there was poor correlation between myelography and the "sensory" level found on clinical examination.

At initial presentation there were always symptoms and signs to raise the suspicion of cord compression. However, diagnosis was delayed after admission to the referring hospital in a number of patients (more than 2 days in 17 men) resulting in further functional loss (Table 2).

Decompressive laminectomy was carried out in all cases and most procedures involved the thoracic spine. There were three peri-operative deaths (8.1%). Thirty-four men were discharged from the neurosurgical unit. Seventeen died in the first year and all but three within 6 months of laminectomy. Thereafter mortality rates were lower and 30% were alive at 2 years and 26% survived 3 years.

Table 2 Deterioration after Presentation before Diagnosis. (N = 33: 4 were Admitted Directly to Neurosurgeons)

Mobility	Improved	0		
	Unchanged	23		
	Deteriorated	10	—ambulant becoming non-ambulant	9
			—paraparetic becoming paraplegic	1
Bladder function	Unchanged	25		
	Deteriorated	8		

Functional results were considered in terms of mobility, bladder function and pain relief.

Seven men were walking before operation; none was made worse and all remained ambulant (Table 3). Twenty-seven were not ambulant before decompression. Seven made an early recovery and could walk at discharge from hospital. A further six made a late recovery and were ambulant when discharged home. Of the 20 men who could walk after laminectomy, 15 remained mobile until death or 1 January 1985, if still alive. Five became non-ambulant again before death but all were able to walk for a significant proportion of the time left to them (1, 3, 7, 12 and 65 months).

Table 3 Ambulatory Status before and after Laminectomy

	Pre-operatively	*Post-operatively*
Ambulant	7	7 (unchanged) 7 (early recovery) 6 (late recovery)
Non-ambulant	27	14

Before laminectomy, 18 patients required a urinary catheter. Nine of these men made sufficient recovery to have this removed. Ten men were symptomatic before operation and although six were unchanged, four regained normal function. Six men with normal pre-operative function were unaffected by laminectomy.

Thirty-four men complained of back pain on presentation. Decompression failed to relieve pain in eight subjects (23%) sufficiently to stop the use of narcotic analgesics. However, pain was significantly relieved in the remainder. Three patients who survived more than 6 months, who were non-ambulant and required a urinary catheter, gained useful long-term pain relief from this procedure.

Those men with previously undiagnosed and therefore untreated carcinoma of the prostate (11) did particularly well. Ten such men survived laminectomy. Seven were non-ambulant before operation but were able to walk afterwards; two men ambulant before operation remained so (Table 4).

Table 4 Recovery of Mobility in Survivors and Pre-operative Treatment

	No.	*Ambulant after laminectomy*
Previously undiagnosed	10	9
Previously diagnosed: no hormonal manipulation	5	3
Previously diagnosed: "hormone escaped"	19	8

All 10 lived more than 2 years; five are still alive and the three longest survivors, at 5 years, had occult disease.

Discussion

In 1953 Kawerichi and Rider stated that "paraplegia caused by metastatic lesions of the vertebrae from carcinoma of the prostate is uncommon". Their report brought the number of such cases in the then recent literature to a total of eight. Twenty-one years later Rubin *et al.* (1974) reviewed 152 men with carcinoma of the prostate seen over 3 years. Forty-nine (32%) were found to have vertebral metastases at presentation and 18 of these (11.8% of the series) presented with a neurological deficit in the legs. Other recent publications (Livingston and Perrin, 1978; Dunn *et al.*, 1980; Constans *et al.*, 1983; Jameson, 1983) have confirmed that metastatic carcinoma of the prostate is a relatively common cause of spinal cord compression and that survival may be prolonged with useful functional improvement after treatment.

None of the 34 survivors was made worse by laminectomy and most received some benefit. On review it has been possible to determine which pre-operative factors were associated with a good outcome following laminectomy. Ability to walk at the time of operation is a favourable factor. Seven (19%) were ambulant before laminectomy and they remained ambulant and all were long-term survivors. Ability to walk at the time of treatment is dependent upon early detection and the diagnosis of impending cord compression must always be considered in patients with carcinoma of the prostate and unremitting back pain. Previously undiagnosed prostate cancer was another favourable factor.

Poor results were associated with an onset of immobility in less than 24 h and with the establishment of paraplegia prior to laminectomy. Seven patients had such an acute onset of loss of functional motor power and six made no recovery. The remaining patient, however, is alive and walking after 18 months. Paraplegia was a consistently accurate indication of poor prognosis. None of these men made any functional recovery and they continued to require narcotic analgesia.

Is laminectomy justified? The general condition of the patient must be taken into consideration: the group reviewed here is biased in that only those considered fit enough for the procedure were referred and accepted for laminectomy. Having established this condition, our results indicate that only patients with paraplegia received no benefit at all from surgery. Until further prospective research justifies another approach, we would advocate laminectomy in all other cases, even if only to relieve pain, because the results often surprisingly justify the means.

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The Authors

J. W. Iacovou, BM, BS, formerly Senior House Officer, Department of Urology, Southmead Hospital. Now Registrar, Department of Urology, University Hospital, Nottingham.

J. C. Marks, FRCS, Registrar, Department of Neurosurgery, Frenchay Hospital.

P. H. Abrams, MD, FRCS, Consultant Urologist, Southmead Hospital.

J. C. Gingell, FRCS, Consultant Urologist, Southmead Hospital.

A. J. Ball, MD, FRCS, Consultant Urologist, Southend Hospital, Westcliff-on-Sea.

Requests for reprints to: J. W. Iacovou, Department of Urology, University Hospital, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH.

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The Fluid Bridge Test Applied to Urethral Sphincter Function with Special Reference to the Male Urethra

A. D. DESMOND, G. R. RAMAYYA and T. K. COWELL

Department of Urology, Broadgreen Hospital, Liverpool and Bioengineering Department, Rayne Institute, St Thomas' Hospital, London

Summary—A new method of performing urethral pressure profiles and fluid bridge tests using computer technology is described, demonstrating the advantages over standard equipment. The fluid bridge test has been used to detect bladder neck incompetence in the male both before and after bladder neck surgery and has been adapted to investigate sphincter weakness at the distal urethral sphincter. This study suggests that the fluid bridge test is useful in the urodynamic evaluation of retrograde ejaculation, post-prostatectomy incontinence and vesico-urethral neuropathy.

The first reported measurements of urethral pressure were described by Bonney (1923). The idea of using a fluid-perfused catheter to measure sphincter pressures was introduced by Pope (1967) for studying the gastro-oesophageal sphincter.

In 1969, Brown and Wickham applied the same technique for measuring pressures within the urethra. In this method, a fluid-perfused catheter with side-hole, connected through a side arm to a pressure transducer, was withdrawn slowly through the urethra. The pressure trace produced was referred to as the urethral pressure profile (UPP). In 1970, Harrison and Constable improved on this technique by incorporating a rotation potentiometer to act as a displacement transducer, which with an XY recorder gave positional sense to the recording catheter.

Brown and Sutherst (1979) developed the fluid bridge test (FBT) for detecting bladder neck incompetence, adding a new dimension to the usefulness of urethral pressure measurements. The test is based on the concept that if urine escapes from the bladder into the proximal urethra during coughing a "fluid bridge" will be created which results in an equalisation of pressure between these two points. The test requires the use of a storage cathode-ray tube owing to the rapid pressure change during coughing. The method of placing the urethral catheter and checking for subsequent catheter shift has been open to criticism and the presentation of the results has generally been unsatisfactory.

Except for a small study by Yalla *et al.* (1982), all fluid bridge tests have been carried out on the proximal urethral sphincter in females with stress incontinence.

To avoid these problems, a new fluid perfused system was designed, based on the modification of Harrison and Constable (1970) and the use of a microcomputer. The apparatus consists of a motorised catheter withdrawal apparatus with an in-built displacement transducer and dual surface-mounted pressure transducers. The XY recorder and storage cathode-ray tube have been replaced by a BBC microcomputer with appropriately designed software and a dot matrix printer. The system is designed so that a fluid bridge test can be performed at any point along the urethra as defined by the static urethral pressure profile. We present our experience with this method.

Patients and Methods

Patients suitable for study were asked to attend the

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985.

urodynamic unit with a full bladder and a free flow rate was performed. This was followed by catheterisation with a double lumen catheter designed to measure bladder and urethral pressures simultaneously (Portex Limited). The residual urine was measured and 200 ml of saline infused into the bladder. The catheter lumina were connected to the dual surface-mounted pressure transducers on top of the motorised withdrawal apparatus, which was positioned to coincide with the level of the symphysis pubis of the supine patient. The bladder catheter was flushed through and the urethral catheter perfused with saline at 2 ml/min. The catheter was then withdrawn along the urethra by the motorised withdrawal apparatus at a constant speed which could be varied from 0.1 to 0.5 cm/s. The urethral pressure profile was displayed on the computer monitor as it was produced.

On completion, the operator can move four vertical cursors to specific points on the profile, thus enabling the computer to record the total bladder pressure (BP), the site of the bladder neck (BN), the highest point of the prostatic plateau (PP) and the pressure at the distal sphincter peak (DS). The computer then calculates the urethral closure pressure (UCP), the distance from the bladder neck to the distal sphincter peak (BN-DS) and the catheter withdrawal speed (WS). For the female there are only three vertical cursors as there is no prostatic plateau to measure, but the computer automatically casts a horizontal cursor from the bladder neck distally to cross the descending curve of the profile to calculate the functional length of the urethra (UCL). The procedure is completed by printing a permanent record of the displayed results on paper using a dot matrix printer. The print-out includes the patient's name and details, the urethral pressure profile tracing and all of the quantitative results.

The procedure for the fluid bridge test commenced by reinserting the double lumen catheter into the bladder. The catheter was withdrawn in the same way until it reached the desired point. Three vertical cursors were then positioned to identify a point within the bladder, the bladder neck and the stopping point in the urethra and the displayed information was printed out as a record of the site where the FBT would be carried out. The fluid perfusion was stopped, making the urethral catheter insensitive to change in pressure transmitted from or through the urethral wall until a fluid bridge was created from the bladder. The operating mode of the computer was now changed from an XY recorder to a YT recorder. The patient was asked to cough, during which the pressures within the bladder and urethral catheters were recorded and displayed graphically on the computer monitor. Since the information was stored by the computer, the time base could be altered to give the most appropriate visual display of the results. The y axis was calibrated to display pressure changes from 0 to 100 cm H_2O, but if the cough pressure exceeded 100 cm H_2O, the computer automatically rescaled from 0 to 200 cm H_2O.

The tracings of the FBT were then printed along with a record of the total bladder pressure, the resting pressure in the urethra at the point where the FBT was performed (USPP), the distance of the FBT from the bladder neck (BN-SP), the values of the maximum cough pressure recorded in the lumina of the bladder catheter (CP) and urethral catheter (UP) and the pressure difference (Fig. 1).

At the end of the procedure the fluid perfusion was recommenced and the UPP program re-run but this time without moving the catheter. A horizontal line was drawn which represented the pressure within the urethra at its post-FBT position. This could be compared with the urethral stopping point pressure to determine any catheter shift. If there was a significant discrepancy, the profile distal to the stopping point could be completed to determine the extent of the catheter shift (Fig. 2).

Results

Sixty-four patients underwent UPP and FBT as part of their urodynamic assessment. Eighteen were female, 10 of these being investigated for stress incontinence and 8 for urethral dilatation. Of the 46 males, 16 had bladder neck obstruction or had undergone bladder neck surgery, 11 had had a transurethral prostatectomy, 6 had post-prostatectomy incontinence and 13 had vesico-urethral neuropathy.

The FBT was negative in all eight females with outflow obstruction before urethral dilatation and in the four tested after dilatation. Of the 10 females with proven stable stress incontinence, 7 had a positive FBT in the supine position. The negative FBTs occurred in three women who had demonstrable stress leakage only while standing and coughing with a full bladder.

An FBT across the bladder neck was performed on 16 males with bladder neck obstruction. All 10 patients studied before surgery had negative FBTs. All nine patients treated by unilateral bladder neck incision continued to show a prostatic plateau and had a negative FBT. Of the two patients treated by

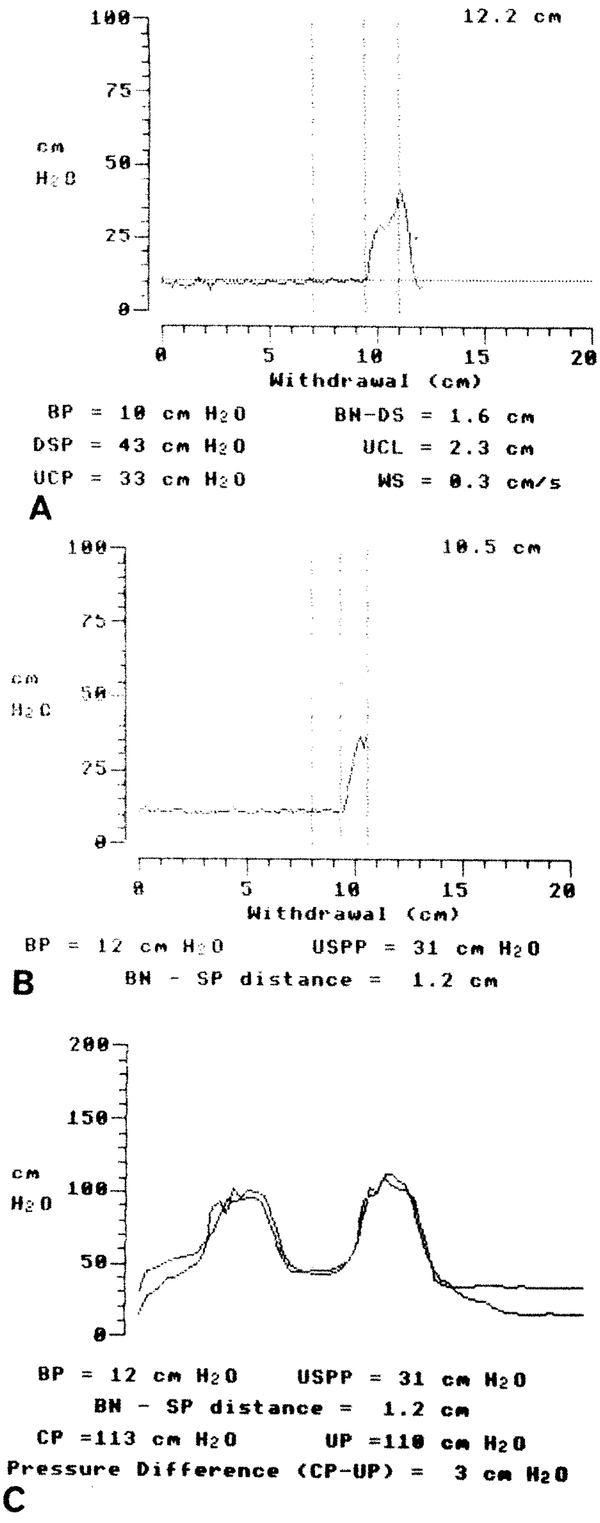

Fig. 1 Three traces of female (JH) with stress incontinence demonstrating (A) UPP. (B) Point on profile where FBT will be performed. (C) Positive FBT.

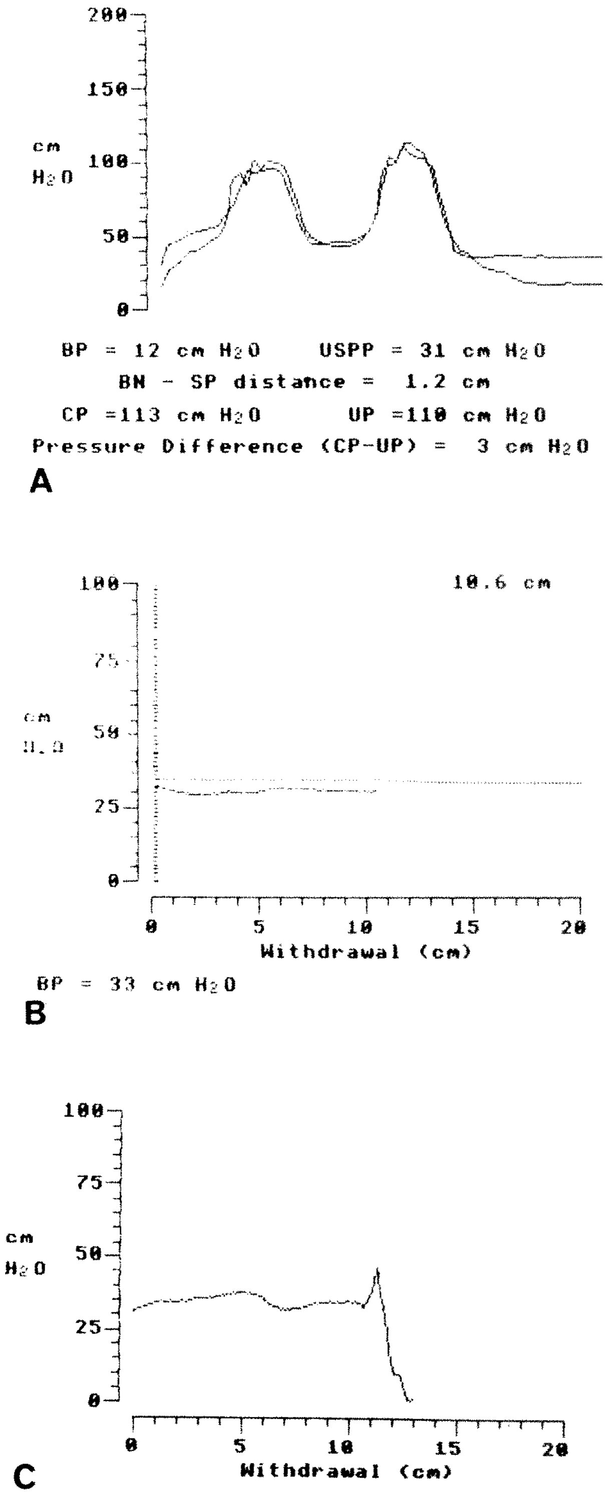

Fig. 2 Three traces of female (JH) showing (A) Positive FBT. (B) Pressure in urethra after FBT for comparison with USPP. (C) Completion of profile distal to the stopping point showing catheter position just proximal to the distal sphincter peak.

bladder neck resection, one had a positive FBT. Three patients were studied specifically because their bladder neck incision had been complicated by retrograde ejaculation; the FBT was negative in all three, but the length of the prostatic plateau was shorter than normal.

To test sphincter incompetence at the distal sphincter, the urethral catheter was positioned just beyond the distal sphincter peak and the patient asked to cough after the fluid perfusion had been switched off—the dry catheter technique. Alternatively, the urethral catheter was positioned beyond the distal sphincter in the bulbar urethra and perfusion was increased to 10 ml/min. At this perfusion rate the catheter is highly sensitive to all changes in pressure transmitted from or through the urethral wall. As the cough impulse is not normally transmitted to the urethra below the pelvic floor, the pressure will rise only if a fluid bridge is created across the distal sphincter (Fig. 3). Of the six patients studied with detrusor-stable post-prostatectomy incontinence, four had positive FBTs in the supine position. Of the 11 males studied after routine prostatectomy, only one had a positive FBT at the distal sphincter and, surprisingly, he did not complain of stress leakage.

There were four positive FBTs in 13 patients with vesico-urethral neuropathy: one at the bladder neck and one at the distal sphincter due to denervation following abdomino-perineal resection, and two at the bladder neck following spinal injury/disease (Fig. 4).

Discussion

The use of computer technology has brought a new era to urodynamic investigation. The apparatus described is not only reliable and effective, but also has considerable advantages over standard equipment. The computer has greatly improved the presentation of the results, which can be displayed both graphically and numerically on a monitor as well as being rapidly committed to print if a permanent record is required. During the fluid bridge test, the system has the ability to check for any shift of position of the catheter that might occur with coughing, without using radiological screening. The possibility of undetected catheter shift has been one of the major criticisms of this investigation. The software progam has included the means to check the calibration of both the pressure and displacement transducers and recalibrate them as required.

The use of the fluid bridge test to assess sphincter competence in the male has important appli-

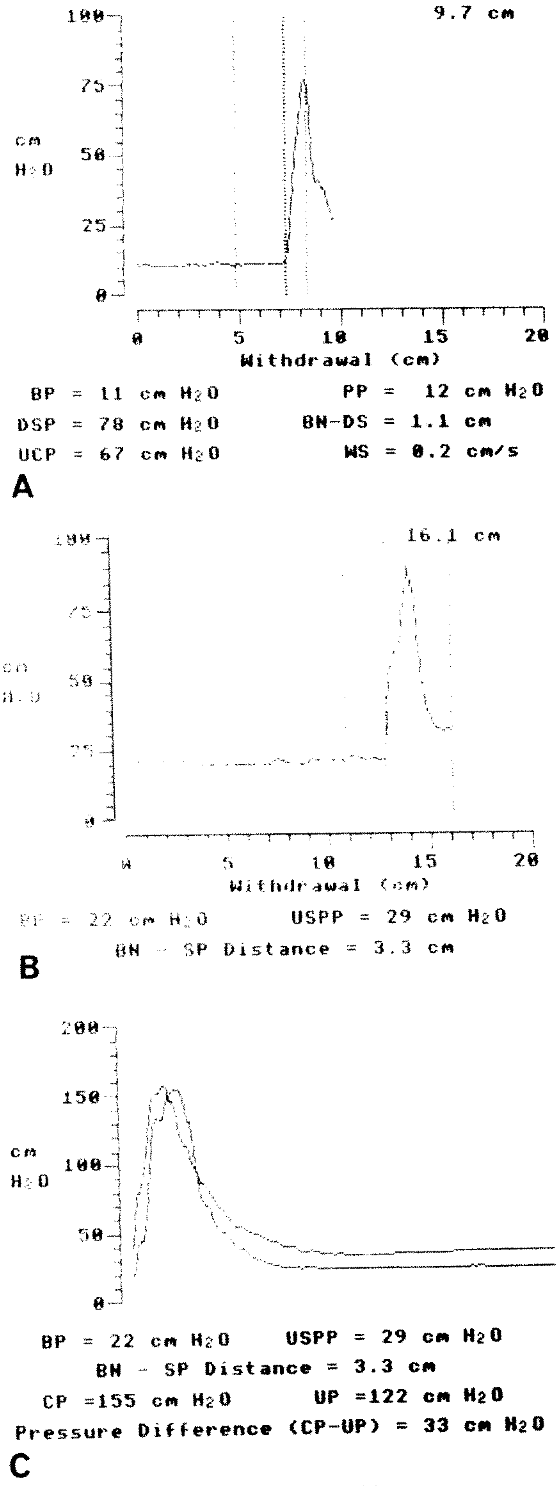

Fig. 3 Three traces of male (TH) with post-prostatectomy incontinence showing (A) UPP. (B) Urethral stopping point beyond the pelvic floor. (C) Positive FBT using wet catheter technique.

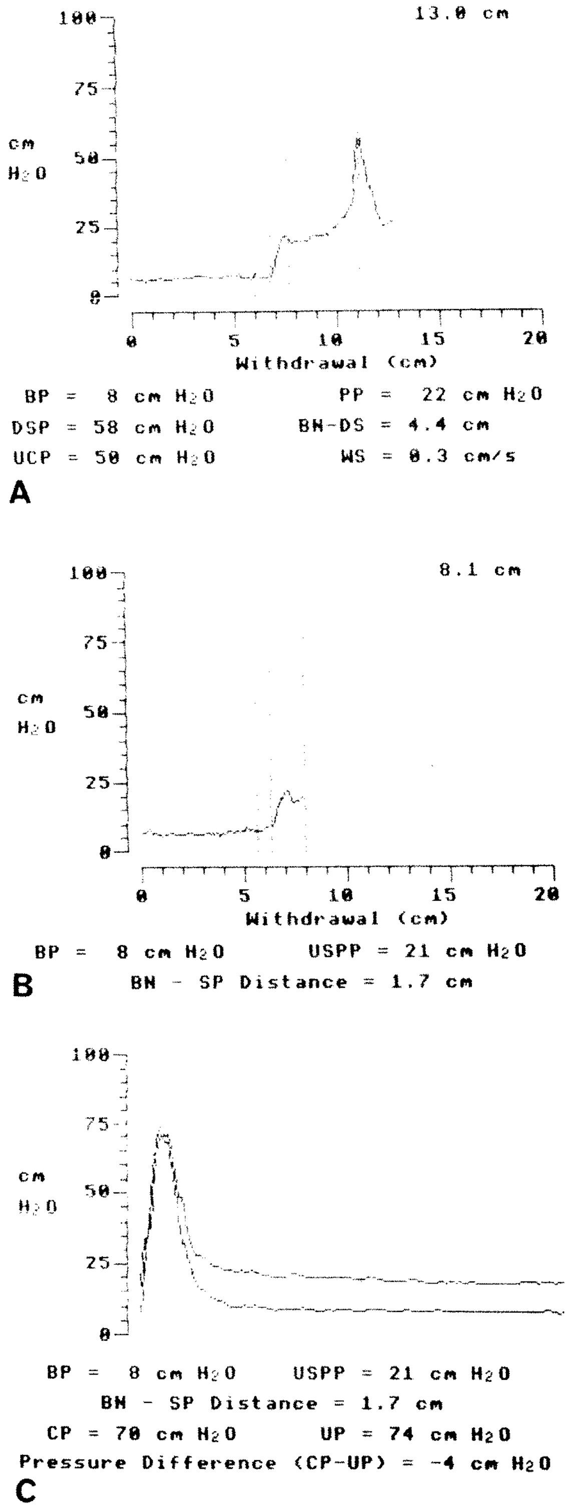

Fig. 4 Three traces of male (GC) with spinal injury showing (A) UPP. (B) Urethral stopping point. (C) Positive FBT across the bladder neck.

cations. Using the FBT, we have shown that unilateral bladder neck incision can relieve outflow obstruction due to bladder neck dyssynergia without significantly weakening bladder neck competence. We have used it to study retrograde ejaculation in patients after bladder neck surgery. We have shown that it can detect stress incontinence in most cases of post-prostatectomy incontinence due to distal sphincter weakness. Although most of these patients were studied in the supine position, the test can be performed in the male with the patient standing.

Probably the main application will be to study sphincter competence in cases of vesico-urethral neuropathy. There were three males in this category who had a positive FBT across the bladder neck. The results were unexpected as the prostatic plateaux on the UPP were intact and no previous bladder neck surgery had been performed. This bladder neck weakness could relate to elevation of the intrinsic detrusor pressure, although this was not apparent at the level of filling used. Also, the change in bladder neck competence may be the result of the direct effect of the vesico-urethral neuropathy. Patients with neuropathic outflow obstruction often require partial or complete distal sphincterotomy. It is predicted that with future FBT studies in these patients, it may be possible to determine whether continence will be preserved.

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The Authors

A. D. Desmond, FRCS, Consultant Urologist, Broadgreen Hospital.

G. R. Ramayya, FRCS, Urological Registrar, Broadgreen Hospital.

T. K. Cowell, Director of Bioengineering, Rayne Institute, St Thomas' Hospital.

Requests for reprints to: A. D. Desmond, Department of Urology, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB.

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Long-term Results of Two-stage Urethroplasty

J. J. F. SOMERVILLE, O. A. ADEYEMI and P. B. CLARK

Department of Urology, General Infirmary and St James's University Hospital, Leeds

Summary—Forty-two patients undergoing a two-stage urethroplasty for stricture were reviewed and the long-term sequelae of 30 patients followed up for a minimum period of 1 year (mean 6.3, range 1-14) are presented.

Twenty-six patients (87%) were considerably improved, with only minor or no symptoms. Three patients (10%) continued to require treatment for urethral stone or recurrence of stricture and one patient was incontinent. The stricture was eradicated in 28 patients (93%).

The late sequelae showed that perineal fistula may not develop until 2 years after the second-stage repair, urethral stone formation until 8 years and recurrence of stricture until 12 years after the second stage. This late onset of sequelae emphasises the importance of long-term follow-up in these patients.

Many operations have been described for the repair of urethral strictures where dilatation or urethrotomy may no longer be approriate, and these may be single or multi-stage procedures. Many make use of an inlay of scrotal skin based on the technique described by Johanson (1953), but the operation is technically difficult and several modifications have been developed to simplify the procedure. Popular amongst these modifications are those described by Turner-Warwick (1960) and Blandy *et al.* (1968), and both procedures have been used since 1968 by one of the authors (PBC). This report reviews the results, particularly with regard to the complications that may develop in the longer term.

Patients and Methods

The hospital notes of the 42 patients who had a urethroplasty performed between 1968 and 1978 were reviewed. The patients' ages ranged from 20 to 78 years (mean 55.4). Details of age, duration of symptoms, aetiology and site of stricture were taken from all patients, but information relating to follow-up and long-term complications relates only to the 30 patients followed up for a minimum of 12 months. Of the 12 patients followed up for less than a year, six have died, four could not be traced, and two were known to have moved.

Table 1 Aetiology of Stricture

Inflammatory	18
Fractured pelvis	5
Post-operative	
Prostatectomy	6
Endoscopies	2
Not stated	11
Total	42

The aetiology of the strictures is shown in Table 1 and their location in the urethra in Table 2. The length of symptoms from these strictures ranged from 1 week to 32 years (mean 11 years).

The nine patients who had their first stage between 1968 and 1971 underwent a Turner-Warwick procedure (Turner-Warwick, 1960); from 1971 the remaining 33 patients had Blandy repairs (Blandy *et al.*, 1968). Two of the Turner-Warwick and six of the Blandy repairs were left as permanent first-stage procedures (Table 3). Four patients

Table 2 Site of Stricture

Anterior urethra	4
Bulb	22
Membranous urethra	8
Full length	6
Not stated	2
Total	42

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Table 3 Reason for no Second Stage

Elderly patient	4
Requested by patient	3
Watering-can perineum	1
Total	8

had routine depilation of scrotal skin before proceeding to the second stage but subsequently this procedure was abandoned. The number of procedures per patient ranged from 1 to 5.

The long-term assessment of the patients was made from the history and urinary flow rates and did not routinely include a urethrogram. Only those patients with a minimum follow-up of 1 year after completion of the second stage were included in this assessment and the mean follow-up period was 6.3 years (range 1-14). Half of the patients have been followed up for 5 or more years (Fig. 1). On the basis of this assessment they were placed into three categories:

(i) Excellent—complete cure of stricture,
no further operative procedure required after the second stage,
no urinary symptoms.

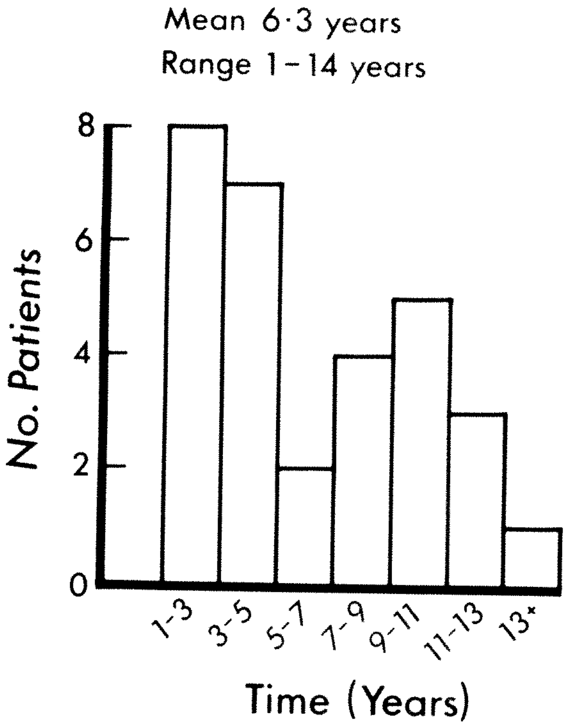

Fig. Distribution of follow-up in 30 patients followed for a minimum of 1 year after second-stage repair.

(ii) Improved—complete cure of stricture,
no further operative procedure required after the second stage, some minor symptoms (*e.g.* post-micturition dribbling, urgency).

(iii) Poor—further surgical procedure required, or incontinence, not present before the first stage.

Results

There were no operative deaths. The overall results of the 30 patients followed up for at least 12 months are shown in Table 4. Patients classified as excellent required no further surgical procedure following the second-stage repair. Patients classified as improved had complete cure of their stricture but complained of post-micturition dribbling (3), stress incontinence (2), occasional urge incontinence (1) and urgency and post-micturition dribbling (1). The eighth patient, although happy with the outcome of his operation, had a slow flow rate on two occasions which he attributed to nerves. He refused any further investigations.

Table 4 Overall Results (30 Patients)

Excellent	16	53%
Improved	8	27%
Poor	6	20%

All patients but one with a poor result required further operative procedures, although in only two was there recurrence of the stricture. Two patients developed a late perineal fistula, two formed calculi in the urethra related to hair growth on the skin inlay (one of whom subsequently developed a further stricture after many endoscopic procedures to remove the urethral stones), one stricture recurred and one patient (who had no further surgery) remained permanently incontinent.

The two patients with a late perineal fistula were reverted to a permanent first stage and there have been no further problems (2 years' follow-up in both patients). The two with urethral stones and the other patient with a recurrent stricture still require endoscopic procedures and the incontinent patient remains so. Thus of the group of six patients, four continue to have problems and two have had no further trouble after conversion to a permanent perineal urethrostomy.

Complications of the first stage (Table 5)

Ten of the 42 patients (24%) who underwent a first stage developed stomal stenosis, especially with the Turner-Warwick procedure, where it occurred in four of nine patients (44%). Seven had revisions of their first stage and three were managed by a single dilatation at the time of the second stage. Three patients complained of incontinence after the first stage which had not been present before. In one, the prostatic urethra split from the verumontanum to the bladder neck when the speculum was being opened during the first stage, and it was felt that this contributed to the incontinence. This patient remained with a permanent dribbling incontinence, while the other two had only mild stress incontinence.

Table 5 Complications of First Stage (42 Patients)

Stomal stenosis	10	24%
Bridging	3	7%
Incontinence	3	7%
Orchitis	2	5%
Impotence	2	5%
Deep vein thrombosis	1	2%

Impotence was recorded in only two patients, but this is probably an inaccurate record. One of these had sustained a fractured pelvis and the other had a watering-can perineum.

Complications following the second stage (Table 6)

The main complaint following the second stage was post-micturition dribbling, which occurred in eight of the 24 patients (33%) undergoing a second-stage repair and for whom long follow-up was available. In three patients this was easily managed but it remained more troublesome in five.

Table 6 Complications of Second Stage (24 Patients)

Post-micturition dribble	8	33%
Incontinence	6	25%*
Perineal fistula	3	13%
Urinary infection	3	13%
Urethral stone	2	8%
Urethral diverticulum	2	8%
Recurrence of stricture	2	8%

* Includes three patients incontinent after first stage.

Three patients developed a perineal fistula; in one it occurred in the immediate post-operative period and settled with further suprapubic drainage: in the other two it occurred later—at 17 months and 2 years. Both patients had poor quality perineal skin: one had a watering-can perineum and chronic lymphoedema of penis and scrotum; the other was a diabetic whose precise skin condition was never recorded. Both patients were eventually converted back to a permanent first stage, after which neither had any further problems.

Three patients complained of incontinence after the second stage, in addition to the three already mentioned in relation to the first stage. In two it settled completely and in the third it improved to manageable urgency.

Only two patients developed a urethral stone, at 3 and 8 years after the second stage. Both required several endoscopic procedures for these stones and this led to a further stricture in one.

Two patients have urethral diverticula; one (the patient whose urethra split during the first-stage repair) is incontinent and the other has post-micturition dribbling. Several of the patients with post-micturition dribbling may have a urethral diverticulum but this was not recorded as such in the notes.

Recurrence of stricture has occurred in two patients, giving a stricture cure rate of 93%. In one, the stricture recurred 7½ years after the second stage following multiple endoscopies for urethral stone formation and in the other it recurred after 12 years, there having been no urethral instrumentation in the intervening period. This latter patient had undergone three urethroplasties but the aetiology of his stricture was not recorded. With these two exceptions, no patient has required urethrotomy or dilatation after the second-stage repair.

Discussion

It is difficult to compare the outcome in this series of 42 patients with that of other series, since there is no uniformity in the way results are presented. A recurrent stricture rate of 7% compares favourably with the rate reported by Smith *et al.* (1978) who had more patients but a shorter mean follow-up of 3.7 years, and it probably stems from the fact that the surgery was performed by one person only (PBC), a point also made by these authors. It also stresses the importance of having the first stage right before proceeding to the second stage, and 17% of the patients required at least one revision of their first stage before undergoing the second stage. A further important point in preventing recurrence, stressed by Colapinto (1969), is that the perineal flap must be taken well clear of the stricture proximally, even if this means dividing the distal sphincter mechanism and bringing the flap to the verumontanum or above. Five patients in this series had the perineal skin flap anastomosed to the verumontanum and while four are completely continent, one is troubled by stress incontinence. In a sixth patient, whose urethra split during the first-stage repair, the perineal flap had to be anastomosed to the bladder neck. He has been incontinent since the operation, though a high anastomosis of the skin flap, even to the bladder neck, does not necessarily affect continence (Blandy, 1974, 1976).

Eight of the 42 patients were known to have had prostatectomies—seven before urethroplasty and one after. One patient was not seen again after the urethroplasty, but the remaining seven had good flow rates and are continent of urine, although three have some minor post-micturition dribbling in the absence of a known urethral diverticulum. In four cases where details of the operation are available, the anastomosis of the perineal skin flap was below the level of the verumontanum.

Although six patients complained of varying degrees of incontinence after their surgery, this has remained a significant problem in only one. In two others it settled completely, a further two have manageable stress incontinence and wear pads for safety, and the sixth has occasional urge incontinence. An additional three patients were incontinent before urethroplasty and remained so after it.

Apart from incontinence, the other serious sequelae associated with urethroplasty, namely perineal fistula, urethral stone and recurrence of stricture, tended to occur late in the follow-up (Table 7), and this emphasises the importance of a lengthy follow-up.

Eight patients were left with a permanent first stage, it never being intended to proceed to the second stage. This group, with a mean age of 69 years and an average history of stricture-related symptoms extending over 17.5 years, did extremely well and were amongst the most grateful of patients. Of the six who have been followed up, five have an excellent result and the sixth, whose flap was taken up to the verumontanum, has some stress incontinence. This is a very satisfactory way of relieving an elderly patient from the rigours of repeated dilatations and anaesthetics and in this regard the poor general health of a patient may be more an indication than a contraindication for such surgery.

Table 7 Late Complications

Complication	*Patients*	*Interval*
Perineal fistula	2	17 months, 2 years
Urethral stone	2	3 years, 8 years
Recurrence of stricture	2	7.5 years, 12 years

Insofar as the aim of urethroplasty is to eradicate stricture without serious side effects, the procedure has been successful in 26 of 30 patients (87%). Only two patients (7%) have required any form of dilatation or urethrotomy after the second stage, and one of these plus one other require treatment for recurrent urethral stones. Only one patient has been rendered incontinent.

It was not possible to identify a particular aetiological group which did well or badly, but it is not surprising that patients with poor perineal skin did badly after the second stage. In our experience this would be an indication for a permanent first stage *ab initio*.

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The Authors

J. J. F. Somerville, MA, MD, FRCSE, formerly Senior Urological Registrar, Leeds and Bradford. Now Consultant Surgeon in Urology, Halifax General Hospital.

O. A. Adeyemi, MB.BCh, Honorary Registrar in Urology, General Infirmary, Leeds.

P. B. Clark, MD, MChir, FRCS, Consultant Urologist, General Infirmary and St James's Hospital, Leeds.

Requests for reprints to: J. J. F. Somerville, Department of Urology, Halifax General Hospital, Salterhebble, Halifax HX3 0PW.

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Surgery for Peyronie's Disease

A Review of 200 Patients

M. J. BAILEY, S. YANDE, B. WALMSLEY and J. P. PRYOR

Institute of Urology, London

Summary—Approximately 10% of patients with Peyronie's disease require surgery for penile angulation or erectile failure severe enough to make coitus difficult or impossible. The results of three different operations performed on 200 patients over the period 1975 to 1984 have been reviewed. The results of plaque excision and dermal grafting in nine patients were disappointing and since 1977, Nesbit's procedure has been performed in 179 patients with excellent results in 53% and moderate results in 19%. Poor results (28%) were usually due to erectile failure and this was usually present pre-operatively. Such patients are better treated by the implantation of penile prostheses and excellent (8) or moderate (2) results were seen in 12 patients so treated. The number of patients with poor results after a Nesbit's procedure increased from 14% at 3 months to 28% at 36 months, but then remained fairly constant. Prolonged follow-up is therefore needed to allow valid conclusions about the ultimate outcome of surgery

Patients with Peyronie's disease commonly present with penile pain associated with an erectile deformity and sometimes impairment of erection. Most patients are able to have intercourse and the disease process usually stabilises and in some patients may even improve. An expectant policy is appropriate, many patients requiring no treatment other than reassurance. Vitamin E or potassium para-aminobenzoate, although neither has been shown to be of benefit in controlled trials, may help to allay anxiety until disease activity ceases. Surgical treatment is indicated in the 10% of patients with sufficient erectile deformity or loss of turgor to make penetration and coitus difficult or impossible.

Patients and Methods

Two hundred patients seen in the Andrology Clinic at St Peter's Hospital, London, between 1975 and 1984 underwent surgery, having satisfied the following criteria:

1. Disease present for at least 1 year.
2. No evidence of disease activity (progression of deformity) for 3 months.
3. Penetration and coitus difficult or impossible.

Plaque excision and dermal grafting (Devine and Horton, 1974) was used initially, but was abandoned in favour of the Nesbit technique (Nesbit, 1965; Pryor and Fitzpatrick, 1979). Most of the deformities were in a dorsal direction and it was necessary to dissect the corpus spongiosum off the corpus cavernosum. The technique has been described elsewhere (Pryor, 1983). The implantation of penile prostheses was initially reserved as a secondary procedure, but has been used as primary treatment in recent years in patients whose main complaint was erectile failure.

Note was made pre-operatively and at follow-up of the angle of deviation of the erect penis (checked if necessary by intracorporeal papaverine), the quality of erections, the amount of difficulty with penetration and coitus, the presence of a plaque and associated pain.

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able 1 Assessment of Results

	Category of results		
ymptom	*Excellent*	*Moderate*	*Poor*
Quality of erection	Normal	Impaired	Absent
Deformity on erection	< 15	15-30	> 30
Coitus	Normal	Possible	Impossible
Shortening of erect penis	< 1 cm	1-2 cm	> 2 cm

In order to be classed as excellent, all criteria must be fulfilled.

Patients were reviewed in the out-patient clinic at 6 weeks, 3 and 12 months post-operatively, and yearly intervals thereafter. Patients not seen recently were contacted by telephone to assess their current erectile status.

The results of operation were classed as excellent, moderate or poor, according to the criteria in Table 1. It should be noted that all patients undergoing surgery would fall into the third category and that a patient in the "moderate " result group would have been improved.

Results

Dermal Grafting

Nine patients underwent plaque excision and dermal grafting. All had poor results and the operation was discontinued (Frank *et al.*, 1981).

Nesbit's Procedure

One hundred and seventy-nine patients underwent a modified Nesbit's procedure between 1977 and 1984. Five patients were lost to follow-up. Table 2 shows the post-operative complications, excluding severe shortening, recurrent deformity and impotence, which are discussed later. Circumcision was performed routinely in patients not already so treated. Of the few patients early in the series in whom this was not done, three required circumcision soon afterwards for preputial oedema leading to phimosis. Patients with symptoms of mild outflow obstruction were catheterised at the end of the operation. Some penile shortening is an inevitable consequence of the operation, but this is no greater than that produced by the disease. Seventeen patients commented on it but were not unduly handicapped. No operative deaths occurred, although three patients are known to have died at 12, 18 and 48 months after surgery. One patient with a haematoma required evacuation and one had a non-absorbable suture in the tunica removed from a persistent sinus. The patient who sustained a urethral injury underwent immediate repair with no long-term sequelae. None of the complications was life-threatening; only 13 patients stayed in hospital for more than 72 h post-operatively, the longest stay being 6 days.

Table 2 Results of Nesbit's Procedure in 174 Men

	Category of result		
	Excellent	*Moderate*	*Poor*
Number	93	32	49
Percentage	53	19	28
Follow-up period (months) ± SD	33 ± 18	31 ± 16	38 ± 19
Range	6-96	6-84	6-92
Age in years ± SD	52.2 ± 12	52.7 ± 10	53.5 ± 11
Range	25-71	20-69	24-70

Five patients lost to follow-up.

Table 3 Complications of Nesbit's Procedure in 174 Patients

Urethral injury		1
Urinary retention		3
Chest infection		5
Haematoma	Moderate	16
	Severe	3
Wound infection		4
Phimosis		3
Numbness of glans		4

Table 3 shows the results of Nesbit's procedure with the age and follow-up period in each category. There was no difference in age or duration of follow-up in the three categories. It was apparent that there was a late deterioration in some patients with an excellent initial result. The proportion of poor results increased from 14% at 3 months to 28% at 36 months (Fig. 1).

Table 4 shows the reasons for failure of Nesbit's procedure, together with the pre-operative quality of erection. Patients who suffered post-operative erectile failure were more likely to have presented with poor erections than patients whose operation failed because of recurrent angulation ($P<0.001$), or those patients whose operation was a success ($P<0.001$). The same is true of patients whose operation failed because of poor erections and angulation ($P<0.05$). Patients whose operations failed because of angulation were less likely to have had erectile problems pre-operatively than those whose operation succeeded ($P<0.05$). Of the patients whose operation was successful, 41% had some degree of erectile impairment pre-operatively.

A similar analysis, comparing the degree of erectile deformity pre-operatively with the reasons for failure, showed no difference between the groups. In four patients, late erectile failure coincided with the onset of severe ischaemic heart disease.

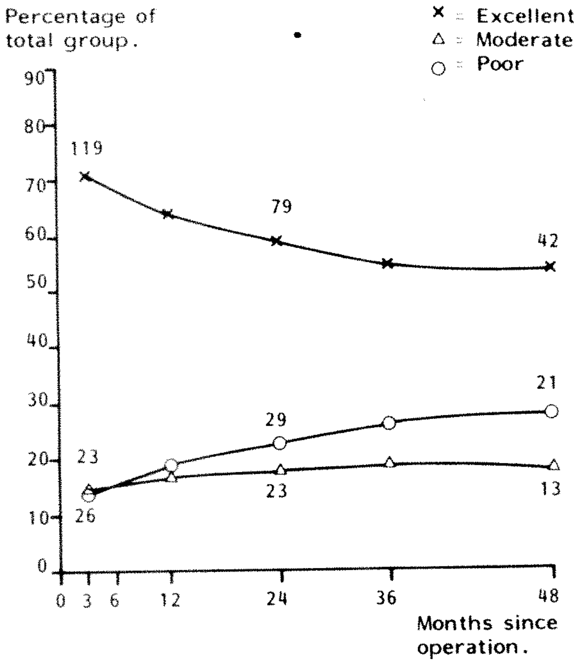

Fig. Change in results of Nesbit's procedure with duration of follow-up.

Penile Prosthetic Implants

Table 5 shows the results of implantation of a penile prosthesis as a primary procedure for patients with impotence due to Peyronie's disease. Two patients had one rod removed for infection. The deformity in these patients remained corrected and one was still able to have intercourse. One patient had both rods removed as he was embarrassed by the permanent erection and his wife had lost interest in sex.

Six patients underwent implantation of a penile prosthesis as a secondary procedure, all for impotence following a dermal graft. Three patients needed implants removing for infection, one rod only being removed in one patient. Results in these three patients were poor, with continuing impotence and angulation. The remaining three patient had satisfactory correction of angulation and reasonable erection.

Discussion

Surgery is necessary only for a small proportion of patients with Peyronie's disease in whom the erectile deformity or lack of stiffness precludes satisfactory coitus. As the the tendency of the natural history of the disease is for stabilisation to occur, sometimes with resolution of the plaque and lessening of the erectile deformity (Mira, 1980), surgery should not be undertaken too early. In this series, stable disease during an observation period of at least 3 months was a prerequisite for surgery.

There have been reports of successful treatment of Peyronie's disease by plaque excision and dermal grafting (Devine and Horton, 1974), but the procedure gave poor results in this series and in others (Melman and Holland, 1978).

Nesbit (1965) described an operation for congenital curvature of the penis which has subsequently been used in patients with Peyronie's disease (Pryor and Fitzpatrick, 1979; Frank *et al.*, 1981; Coughlin *et al.*, 1984; Lemberger *et al.*, 1984). The late follow-up of the present series has shown that early good results of Nesbit's procedure may deteriorate with time. This deterioration may be due either to loss of erectile rigidity in patients with normal erections in the early months after surgery, or to further erectile deviation after initial adequate correction.

Analysis of the results shows that patients presenting with severe impairment or complete failure of erection were likely to have an unsatisfactory outcome due to post-operative persistence of the erectile inadequacy. The degree of angulation of the erect penis pre-operatively had no such predictive effect either for failure related to angulation or erectile failure.

These observations, taken in conjunction with the good results of primary penile implantation for patients with Peyronie's disease causing erectile inadequacy, suggest that when impotence is the predominant symptom, implantation of a penile prosthesis rather than Nesbit's procedure should be performed. The disappointing results of penile implantation for impotence after dermal grafting reinforce this concept; implants are more likely to succeed if the tunica albuginea has not previously been breached surgically.

able 4 Pre-operative Erectile Function in Patients whose Nesbit's Procedure Failed

		Pre-operative erectile status			
eason for failure	*Number*	*Normal*	*Impaired*	*Absent*	*Column*
Poor quality of erection	35	10	22	3	I
Residual or recurrent angulation	20	16	4	0	II
Poor erection and angulation	14	6	7	1	III
Successful operations (for comparison)	93	52	38	3	IV

Columns I *vs* IV $\chi^2 = 7.4$ $P < 0.01$
I *vs* II $\chi^2 = 16.2$ $P < 0.001$
II *vs* III $\chi^2 = 8.6$ $P < 0.01$
II *vs* IV $\chi^2 = 6.1$ $P < 0.05$

In addition, seven patients had poor results due to penile shortening and three had poor results due to persisting pain.

Table 5 Results of Penile Implants in 18 Men

		Penile implants for Peyronie's disease	
		Primary	*Secondary*
Number		12	6
Follow-up period			62 ± 21.2
Mean ± SD (months)		26 ± 9.2	62 ± 21.2
(Range)		(6-48)	(24-96)
Results	Excellent	8	3
	Moderate	2	0
	Poor	2	3

We conclude that Nesbit's procedure is safe and effective in correcting the angulation due to Peyronie's disease. Patients complaining of impotence or severely impaired erections pre-operatively are likely to continue to have erective failure post-operatively and should be treated by implantation of penile stiffening rods.

Early post-operative results may be misleadingly good, and prolonged follow-up is needed to identify late failures.

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The Authors

M. J. Bailey, MS, FRCS, Senior Registrar, St Peter's Hospital, London.

S. Yande, FRCS, Senior House officer, Department of Urology, Southmead Hospital, Bristol.

B. Walmsley, FRCS, Consultant Urologist, St Mary's Hospital, Portsmouth.

J. P. Pryor, MS, FRCS, Consultant Urologist, King's College Hospital and St Peter's Hospital, London.

Requests for reprints to: M. J. Bailey, St Peter's Hospital, Henrietta Street, London WC2E 8NE.

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Serum and Tissue Tumour Markers in Seminomas

T. F. FORD, D. N. BUTCHER, C. T. SAMUELL, J. R. W. MASTERS, M. CONSTANCE PARKINSON and R. T. D. OLIVER

St Peter's Hospitals and Institute of Urology, London

Summary—The serum expression of the tumour markers hydroxybutyric dehydrogenase (HBD), beta human chorionic gonadotrophin (βHCG), alphafetoprotein (αFP) and placental alkaline phosphatase (PLAP) has been assessed in a consecutive series of 50 patients with pure seminoma. In pre-orchiectomy sera from 15 patients with stage I disease, HBD was elevated in 5, βHCG in 3, αFP in 1 and PLAP in 1 (of 3 only). In 27 patients with stage 2 or 3 disease, prior to chemotherapy, serum HBD was elevated in 19, βHCG in 11, αFP in 2 and PLAP in 10 (of 18). The presence of βHCG was investigated immunocytochemically in primary tumour tissue from 39 patients. It was demonstrated in 6 of 21 tumours from patients with stage I disease and 5 of 18 with stage 2 or 3 disease.

The frequency and significance of serum alphafetoprotein and beta human chorionic gonadotrophin in non-seminomatous germ cell tumours are well documented (Sidi *et al.*, 1984). In pure seminomas the situation is less clear, both with regard to these and other potential markers such as placental alkaline phosphatase (Jeppsson *et al.*, 1983) and hydrobutyric dehydrogenase (Lippert and Javadpour, 1981). In addition, the significance of the immunocytochemical demonstration of βHCG-containing giant cells in seminomas, both in terms of prognosis and the serum expression of this glycoprotein, are yet to be established (Butcher *et al.*, 1985). The present study was designed to investigate these questions in a consecutive series of patients managed in one unit.

Patients and Methods

In the period 1979 to 1984, 50 patients with testicular seminoma were referred to the Oncology Unit of the Institute of Urology (under the care of RTDO). Staging investigations, including chest X-ray, thoracic and abdominal CT scanning, were performed on all patients. Twenty-two patients were thus classified as having stage I disease, 16 stage 2 (a-2, b-2, c-12) and 12 stage 3 (all 3c). Of the patients with stage 2 or 3 disease, four had developed recurrent disease following abdominal irradiation at another hospital prior to referral; the remainder had received no treatment (other than orchiectomy). Tumour marker assays (HBD, αFP, βHCG and PLAP) were performed on all patients (PLAP assay has been available only since 1982) where possible prior to orchiectomy or commencing chemotherapy, and serially thereafter.

Following orchiectomy, initial treatment in patients with stage I disease consisted of abdominal irradiation up to 1982. Since then, such patients have been the subject of a surveillance policy (Oliver *et al.*, 1983). Initial treatment of patients with metastatic disease was BVP (bleomycin, vinblastine, cisplatin) until 1981 and, thereafter, cisplatin alone (Oliver *et al.*, 1984). During the early phase of follow-up, tumour markers were estimated at monthly intervals and the CT scans repeated at 3-monthly intervals.

Tumour Marker Assays

PLAP Placental alkaline phosphatase was estimated using a monoclonal antibody in an ELISA

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ble 1 Serum Tumour Markers in Seminomas. The Numbers of Patients with Significant Elevations Prior to rchiectomy in Stage 1 Disease and Post-orchiectomy, Pre-chemotherapy in Stages 2-3

	HBD (iu/l) *>180*	*βHCG (iu/l)* *>60*	*PLAP (OD)* *>0.2-0.4*	*αFP (u/ml)* *>10*
Stage 1	5/15	3/15	1/3	1/15
Range	190-306	72-162	1.14	45
Stages 2-3	19/27	11/27	10/18	2/27
Range	319-6400	138-3000	0.36-1.92	17, 1800

assay, the specificity and sensitivity of which have been previously reported (Tucker *et al.*, 1985). Because of false positives in smokers an optical density (OD) of 0.2 was considered the upper limit of normal for non-smokers and 0.4 for smokers.

βHCG and αFP were both determined by standard radioimmunoassay procedures, the former using a double-antibody method, the latter a polyethylene glycol precipitation technique. The current adult reference ranges for βHCG are <15 iu/l and <10 u/ml for αFP. Because some of the samples prior to 1982 were processed using a less sensitive assay, <60 iu/l has been used as the upper limit of normal for βHCG in this study.

Hydroxybutyric dehydrogenase (HBD) was assayed using a routine reaction rate technique at 340 nm and 37°C. Haemolysed specimens were not analysed. The adult reference range was 72 to 182 iu/l.

Immunocytochemical localisation of βHCG The presence of βHCG-containing cells was demonstrated immunocytochemically in formalin fixed and paraffin-embedded material using a peroxidase-anti-peroxidase technique, full details of which have been published elsewhere (Butcher *et al.*, 1985). Histological specimens from 39 patients (39 testicular primaries) were available for analysis.

Results

Patients presenting with stage I disease

Serum was available for marker estimation in 15 of 22 patients prior to orchiectomy (3 only in the case of PLAP) (Table 1). The marker most commonly elevated was HBD in five patients, two of whom also had raised βHCG and one PLAP levels. This last patient had normal βHCG. In none was the level grossly elevated and in all 22 patients serial estimations of all markers remained normal throughout follow-up.

In tumour tissue from six of 21 patients, βHCG was demonstrable immunocytochemically—in syncytiotrophoblastic giant cells in four and in mononuclear seminoma cells in two. In four of these patients, pre-orchiectomy serum estimations of βHCG were made, only one of which was elevated.

Patients presenting with metastatic disease

Serum tumour markers obtained after orchiectomy and before chemotherapy were available from 27 of 28 patients (Table 1). The most consistently elevated marker was HBD (19 of 27, 70%) and in eight patients was the only raised marker. Levels of PLAP were elevated in 10 of 18 patients (56%) and in all of these HBD was also high.

Twenty-two patients went into complete remission following initial courses of chemotherapy and in all cases elevated serum markers, where present, returned to normal values. Of these 22 patients, three subsequently developed recurrent disease requiring further chemotherapy and are now alive and disease-free. One of these patients was consistently serum marker negative and relapse was proven by supraclavicular node biopsy. In the remaining two, both initially and during relapse, disease activity was reflected in raised serum HBD.

Six patients failed to respond to their initial chemotherapy as judged by persistently high tumour markers in four and by CT scanning in all six. One was found to have mature teratoma in an excised residual mass and remains alive and well. The remaining five died, one from complications of bleomycin therapy rather than his disease. Table 2 summarises marker and clinicopathological details. Before treatment, two of these patients had raised levels of αFP and two raised βHCG and one was marker negative. One developed raised levels of αFP following partial response to chemotherapy during regrowth of drug-resistant disease, and at this stage biopsy showed the development of non-seminomatous germ cell tumour (NSGCT).

In the patients with metastatic disease, 5 of 18

Table 2 Serum Levels of Tumour Markers (Maximum Recorded Values) in Patients who Failed to Respond Chemotherapy. N = normal

Patients	*HBD (iu/l)*	*βHCG (iu/l)*	*PLAP (OD)*	*αFP (u/ml)*	*Tissue βHCG*	*Cause of death*
A.J.	N	N	N	N	– ve	Seminoma
N.W.	3637	*1800	1.92	*350	+ ve (mononuclear)	Seminoma (testis) MTU (nodes—biopsy)
D.S.	943	300	1.4	17	– ve	Seminoma (post mortem)
F.N.	2878	925	2.0	N	– ve	Seminoma (post mortem)
N.B.	214	N	N	1800	+ ve (giant cell)	Bleomycin lung (biopsies) Seminoma

* Recorded during development of drug resistant disease.

primary tumours had immunocytochemical evidence of βHCG staining—two in syncytiotrophoblastic giant cells and three in mononuclear seminoma cells. Two of these five gave rise to nodal metastases containing NSGCT elements.

Correlation between tissue and serum

The relationship between the presence of βHCG-containing cells in primary tumours and the serum expression of this marker is shown in Table 3.

Table 3 Relationship between Serum Expression of βHCG and the Presence of βHCG-Containing Cells in Seminomas (Stages 1, 2 and 3)

		Serum		
		Positive	*Negative*	*Totals*
Tissue	Positive	3	6	9
	Negative	8	16	24
	Totals	11	22	33

There were 33 patients in whom pre-orchiectomy (stage 1) or pre-chemotherapy (stages 2 or 3) sera could be compared to the presence of βHCG-containing cells. Of the 9 tissue-positive tumours, elevated levels of βHCG were detectable in only 3 cases, while 8 of 11 serum positives did not have βHCG detectable in the sections which were examined.

Discussion

Serial estimations of serum markers are routinely used to monitor therapeutic response, although none of the available markers is either specific for or universal to all testicular germ cell tumours (Lange and Raghavan, 1983). In this series of 50 seminomas, elevated levels of at least one serum marker were present in approximately 40% of patients with disease confined to the testis and 75% of patients with metastatic tumour. Absolute levels varied, but increased with stage, and changes shown in serial measurements reflected both response to treatment and recrudescence of disease.

Hydroxybutyric dehydrogenase was the most consistently raised marker; the frequency of its elevation in both stage 1 and metastatic disease corresponded to that reported by other workers (Lippert and Javadpour, 1981). Of the five circulating isoenzymes of lactate dehydrogenase (LD), some (notably isoenzymes 1 and 2) reacted preferentially with hydroxybutyrate as a substrate. Thus, the assay of serum hydroxybutyric dehydrogenase (HBD) was an attempt to achieve some index of the level of these isoenzymes. However, maximum selectivity for isoenzymes 1 and 2 is achieved by running the assay at 25°C, so much of this selectivity would be lost in an assay performed at 37°C, and the results would essentially be the same as those obtained from total serum LD estimation. It is important to remember the ubiquitous distribution of LD in tissues and therefore the non-specificity of the serum measurement. Isoenzymes 1 and 2 predominate in myocardium (the main use of the HBD assay being the assessment of myocardial damage), erythrocytes, bone marrow and kidney, while high levels of the other isoenzymes occur in liver and skeletal muscle. Levels can therefore be raised in association with malignancies or tissue damage in many organs (Papadopoulos, 1977). These points need to be considered when interpreting serial tumour marker studies.

Levels of PLAP were raised in 56% of patients with stage 2 or 3 disease, a figure similar to that quoted in earlier reports (Lange *et al.* 1982; Jeppsson *et al.* 1983). Normal values are higher in smokers and occasional false positives are seen in the normal population (Tucker *et al.*, 1985). When taken in conjunction with HBD measurements, which were always concordantly elevated, PLAP levels were an accurate marker of disease activity.

The finding of elevated levels of αFP resurrects the question of when is a seminoma not a seminoma. Some authors consider that such a finding proves the presence of non-seminomatous elements (Sidi *et al.*, 1984), whereas others suggest that it merely represents the histological continuum observed in testicular germ cell tumours (Raghavan *et al.*, 1982).

The poor correlation between the immunocytochemical demonstration of βHCG-containing cells and circulating levels in peripheral blood may be the result of histological sampling. In some cases the results are based on sections referred from other hospitals, and these may not be representative of the whole tumour. It is also possible that formalin fixation may prevent βHCG staining in tissue, as has been suggested for αFP (Raghavan *et al.*, 1982). However, this possibility was not confirmed in comparisons of βHCG staining in a series of fresh frozen and paraffin sections of the same tumour, which gave similar results in our laboratory (unpublished observations). Conversely, although βHCG is detected in tissue, it may be produced in quantities too small to appear in the peripheral blood, as indicated by the thorough study of Masuda (1982). This investigation of 25 seminomas demonstrated βHCG-containing cells immunocytochemically in 45%, βHCG in peripheral blood in 48%, in testicular vein blood in 89% and in tissue homogenates in every case. It is apparent that HCG production by seminomas is much more common than originally supposed on the basis of observations of syncytiotrophoblastic giant cells in haematoxylin and eosin sections (Thackray and Crane, 1976) and that immunocytochemical demonstration underestimates the proportion of tumours containing HCG.

There is evidence that prognosis is worse in seminoma with elevated serum levels of βHCG (Morgan *et al.*, 1982) or βHCG-containing cells demonstrated immunocytochemically (Butcher *et al.*, 1985). In contrast, other studies on small numbers of patients with seminoma concluded that elevated levels of circulating βHCG do not alter the prognosis (Mauch *et al.*, 1979; Swartz *et al.*, 1984; Steffens *et al.*, 1985). In our study the one patient with stage 1 disease who relapsed after 2 months' surveillance had βHCG-containing giant cells in his tumour. The presence of such cells should alert the clinician to the possibility of a non-seminomatous tumour, since two of the six positive-staining tumours in the stage 2 or 3 group gave rise to nodal deposits containing teratomatous as well as seminomatous elements.

The relative rarity of this disease, coupled with rapid advances in successful therapy, make the question of the prognostic significance of βHCG in seminomas difficult to answer. The balance of evidence indicates that βHCG in seminomas is associated with slightly more aggressive disease, but that over 90% of all metastatic seminomas respond to chemotherapy (Schuette *et al.*, 1985). In the light of these observations, it is our current practice to use cisplatin alone for metastatic seminoma patients without evidence of βHCG and αFP production (Oliver *et al.*, 1984) and treat the βHCG- and αFP-producing tumours with the standard teratoma chemotherapy (bleomycin, etoposide and cisplatin), until the long-term follow-up confirms the safety of using single agent cisplatin.

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The Authors

T. F. Ford, MA, DM, MCh, FRCS, formerly Senior Registrar in Urology, St Peter's Hospitals. Now Senior Registrar, Royal United Hospital, Bath.

D. N. Butcher, MIMLS, Medical Laboratory Scientific Officer, Institute of Urology.

C. T. Samuell, MCB, Principal Biochemist, St Peter's Hospitals and Institute of Urology.

J. R. W. Masters, PhD, Senior Lecturer in Histopathology, Institute of Urology.

M. Constance Parkinson, BSc, MD, MRCPath, Consultant Histopathologist, St Peter's Hospitals and the Institute of Urology.

R. T. D. Oliver, MD, MRCP, Senior Lecturer in Oncology, Institute of Urology and Sir Maxwell Joseph Reader in Medical Oncology, London Hospital Medical College.

Requests for reprints to: T. F. Ford, Department of Urology, Royal United Hospital, Combe Park, Bath BA1 3NG.

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The Accuracy of CT Scanning Prior to Para-aortic Lymphadenectomy in Patients with Bulky Metastases from Testicular Teratoma

C. L. KENNEDY, J. E. HUSBAND, E. A. BELLAMY, M. J. PECKHAM and W. F. HENDRY

Testicular Tumour Unit, Royal Marsden Hospital, London

Summary—The accuracy of CT scanning prior to para-aortic lymphadenectomy was assessed in 108 patients with metastatic testicular teratoma. In 106 its presence was confirmed by surgery. The site was accurately predicted in 95%. A good correlation ($P < 0.0025$) was found between mean tumour cross-sectional area assessed by CT scanning and that measured in the excised pathological specimens.

The role of para-aortic lymphadenectomy to remove residual tissue following chemotherapy for non-seminomatous germ cell testicular tumours is now well established and the results of such surgery have already been reported (Tait *et al.*, 1984). Lymphadenectomy is an essential aid to planning the next stage of therapy as well as being of prognostic value. Reports of sarcomas arising in residual teratoma (Ahlgren *et al.*, 1984) are a further indication for the removal of such tissue. Representative biopsy has been shown to be inadequate (Donoghue *et al.*, 1982) and therefore accurate localisation of the tumour mass is an essential prerequisite for adequate access and complete excision.

Patients and Methods

We studied 108 patients who had undergone removal of residual masses following four or six cycles of chemotherapy for metastatic non-seminomatous germ cell testicular tumours (Peckham *et al.*, 1981, 1983). All patients were assessed with regular serum marker estimations and repeated CT scanning of the metastatic tumour masses (Husband *et al.*, 1981). Surgery was usually performed 4 weeks after completion of chemotherapy, although with some small masses this was delayed until no further shrinkage of the mass was observed; in some cases the mass disappeared, thus eliminating the need for surgery. A scanogram was constructed to define clearly the site and size of the mass (Fig. 1). The kidneys, renal vessels, aorta and vena cava were drawn freehand on a plain abdominal radiograph or urogram picture, demonstrating their relationship to the tumour masses. Cystic or solid areas were marked separately. Alternatively, similar pictures can be constructed directly on to the CT scanner scout film (Fig. 2). Tumour cross-sectional measurements were obtained and compared with the pathological measurement of the resected specimens. The predicted tumour site was compared with the operative findings. Ureteric involvement was assessed by intravenous urography.

Results

In 84 patients the residual mass was localised below the renal vessels (Fig. 3) and resected through a long midline incision. In one of them there was unexpected extension above the renal vessels, though fortunately complete excision could still be achieved. In two patients the mass demonstrated by the scanogram could not be found and in one was considerably smaller than anticipated (Table).

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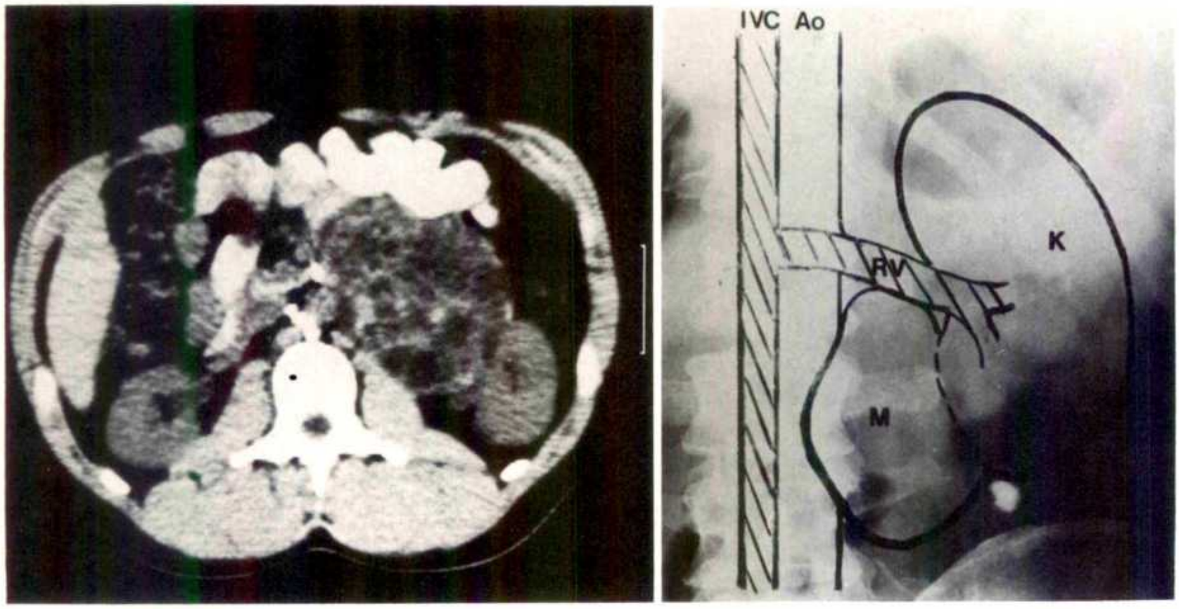

Fig. 1 CT scan and scanogram showing para-aortic metastatic teratoma displacing lower pole of left kidney.

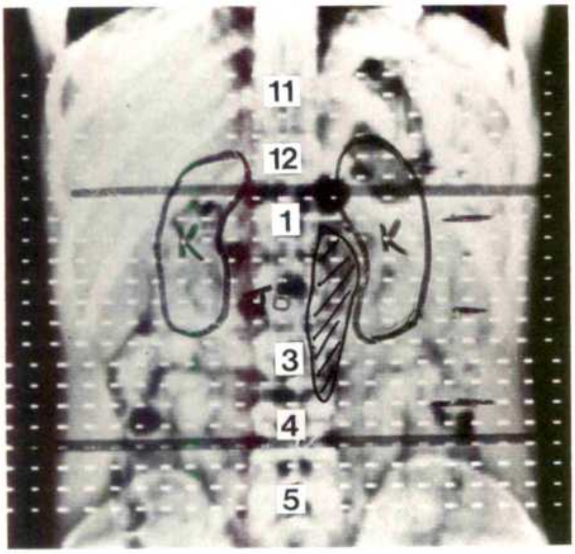

Fig. 2 Scanogram taken from CT film showing tumour to the left of the aorta.

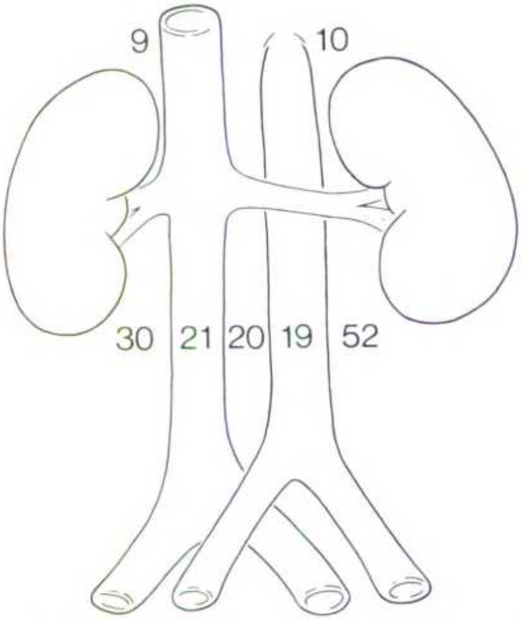

Fig. 3 Sites of resected masses in 108 patients (some had tumour in more than one site).

In the remainder, CT assessment of tumour size correlated well with the measurements of the specimens (Pearson product-moment coefficient of correlation $r = +0.4$ $P < 0.0025$).

In 24 patients a thoraco-abdominal approach was required because of extension above the renal vessels, renal involvement, or large size of the mass; 14 patients had synchronous resection of pulmonary and abdominal metastases. In all but one the masses were accurately localised; in one case there were three small (1 cm) unexpected pulmonary deposits.

Ten patients underwent concomitant nephrectomy on account of involvement of the ureter, kidney or renal vessels and one patient had staged

Table Results of Localisation of Para-aortic Masses in 108 Patients

	No.	*Site accurately localised*	*Site inaccurately localised*
Infrahilar	84	80 (95%)	4 (5%)
Suprahilar	24	23 (96%)	1 (4%)
Total	108	103 (95%)	5 (5%)

abdominal and thoraco-abdominal procedures for widespread metastases.

Discussion

The nature of the residual tissue after chemotherapy determines the prognosis and subsequent therapy in non-seminomatous germ cell testicular tumours. Complete excision of such tissue should be performed if possible, both to obtain accurate histological diagnosis and also for its therapeutic benefits: it appears that patients most at risk are those who have not had a complete resection (Loehrer *et al.*, 1983; Tait *et al.*, 1984). In seminoma, the residual tissue is usually densely adherent to the surrounding structures and complete excision may not be possible and is, in any case, usually unnecessary.

For the clinician, interpretation of body CT is frequently difficult and we have found the scanogram a simple and convenient way to display the relevant findings to the clinical team. Accurate localisation enables the clinician to plan the nature and extent of the surgical procedure, thus permitting optimum use of operating time and support services. In our series we have used a long midline incision where the disease was confined below the renal vessels. This gives good access around the great vessels and below the aortic bifurcation. Waters *et al.* (1982) have advocated the routine use of a thoraco-abdominal incision but this may hinder dissection behind the contralateral great vessels and we have occasionally experienced recurrent active disease at this site due to incomplete resection. Where the mass extends above the renal hilum or there is direct renal involvement, the thoraco-abdominal approach is preferable and ipsilateral pulmonary deposits may be resected at the same time. Though such resections are obviously major undertakings, an acceptable morbidity is associated with the procedure (Skinner *et al.*, 1982; Waters *et al.*, 1982). Despite this, it is often the loss of ejaculation that may occur following dissection around the sympathetic chain or hypogastric plexus that troubles the patient most. This is unlikely to occur with a unilateral resection, but the accurate localisation of the residual tissue will enable patients at risk to be warned.

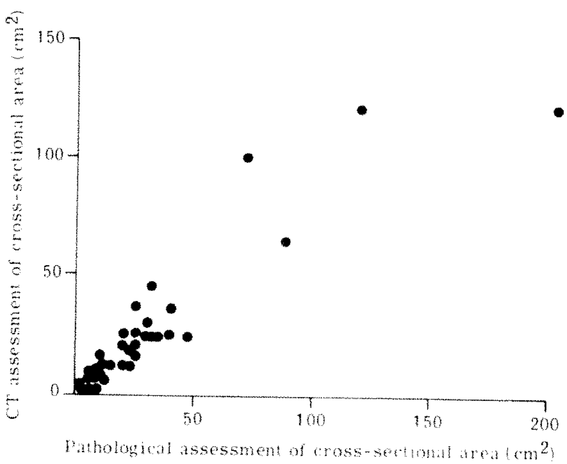

Fig. 4 Correlation between CT and pathological assessment of cross-sectional area of para-aortic masses.

Patients in whom the masses were much smaller than anticipated all had inactive disease histologically which, presumably, had undergone involution in the interval prior to surgery. Dissection was rather more difficult with solid compared with cystic areas and differentiation between them can be obtained by CT scanning. The Hounsfield number may reflect the nature of the constituents of the mass (Husband *et al.*, 1982). The attenuated ureter, which often marks the lateral margin of the abdominal tumour, is not always visualised on CT scanning and we therefore obtain a urogram before resection of para-aortic and para-caval masses. Despite oral contrast enhancement, bowel involvement was difficult to determine by scanning; fortunately this complication was rarely encountered. We regard CT assessment of the great vessels as essential, since involvement of the vena cava may occur with occlusion of its lumen. This is not a contraindication to resection of the mass, for the vena cava may be excised below the renal vessels with little additional morbidity, since a collateral venous return will usually have been established.

It is concluded that CT scanning accurately defines the site and size of residual metastatic disease following chemotherapy for non-seminomatous germ cell testicular tumours. The scanogram is a simple and reliable way of transmitting this information, thus facilitating the planning and execution of the surgical removal of such tissue.

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The Authors

C. L. Kennedy, FRCS, Senior Urological Registrar.
J. E. Husband, MRCP, FRCP, Consultant Radiologist.
E. A. Bellamy, MRCP, FRCR, Consultant Radiologist.
M. J. Peckham, MD, MRCP, FRCR, Professor of Radiotherapy.
W. F. Hendry, ChM, FRCS, Consultant Urologist.

Requests for reprints to: W. F. Hendry, Testicular Tumour Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ.

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Surveillance or Lymph Node Dissection in Clinical Stage I Non-seminomatous Germinal Testis Cancer?

G. PIZZOCARO, F. ZANONI, R. SALVIONI, A. MILANI and L. PIVA

Section of Urologic Oncology, Department of Surgery, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Summary—Surveillance following orchiectomy alone has gained popularity in the management of clinical stage I non-seminomatous germ cell tumours (NSGCT) of the testis. However, long-term follow-up of the retroperitoneal nodes can be difficult.

We analysed the results of 71 consecutive patients followed for more than 1 year. Fifty men (70.5%) remain disease-free and 21 (29.5%) have relapsed. Relapses occurred 2 to 36 months after orchiectomy (median 6 months). Retroperitoneal nodes were involved in 12 cases (17%). In only one patient were retroperitoneal metastases diagnosed when smaller than 2 cm and in four they were diagnosed when larger than 5 cm. Furthermore, the late relapses occurred in the retroperitoneal nodes. After treatment of metastases, 69 patients (97%) are alive, disease-free and off therapy.

As retroperitoneal relapses do not occur after a properly executed retroperitoneal lymph node dissection (RPLND) and ejaculation problems can be avoided with unilateral RPLND, it is suggested that RPLND can be used for clinical stage I NSGCT of the testis in experienced surgical centres, with the advantage of an easier follow-up.

Since 1979, surveillance has gained popularity in the management of clinical stage I non-seminomatous germ cell tumours of the testis. Preliminary results (Peckham *et al.*, 1982; Read *et al.*, 1983; Jewett *et al.*, 1984; Sogani *et al.*, 1984) have shown relapse rates of 17 to 40% and survival rates of 100% after minimum follow-up of 2 to 6 months (median 15-20).

The rationale for surveillance is the improved clinical staging with early detection of metastases by CT scanning (Husband *et al.*, 1981) and serum tumour marker studies (Barzel and Whitmore, 1979), and the high curative potential of chemotherapy in small volume metastatic disease (Einhorn and Donohue, 1977; Peckham *et al.*, 1983). The purpose of surveillance is to avoid unnecessary radiotherapy or retroperitoneal lymph node dissection in a presumed high proportion of patients who can be cured with orchiectomy alone, and to identify patients at high risk of harbouring occult metastases who might benefit from prophylactic treatment (Peckham *et al.*, 1982). The hazard of surveillance is the potentially difficult long-term follow-up of retroperitoneal nodes. For this reason we analysed our patients with a minimum follow-up of 1 year and compared them with data in the literature.

Patients and Methods

Seventy-five consecutive patients with clinical stage I NSGCT of the testis entered the surveillance study from August 1981 to June 1984. Entry criteria were the absence of tumour at the cut end of the spermatic cord, informed consent and full availability for a close follow-up. The patients' ages ranged from 14 to 63 years (median 26). Most of them had had an orchiectomy elsewhere within 2 months. Histological slides were reviewed in all cases and the pathological diagnosis was re-

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assessed. Patients who had had an incision in the scrotum were submitted to *en bloc* resection of the funicular stump and the scrotal scar.

All patients had unequivocally negative physical examination, chest X-ray, bipedal lymphangiography (LAG) and CT of the abdomen. Serum tumour markers (AFP and HCG) were normal after orchiectomy, or they returned to normal, according to their half-life kinetics ($\leqslant 5$ days for AFP and $\leqslant 1$ day for HCG).

Patients were followed up monthly during the first year, bi-monthly during the second year and every 3 months thereafter, with repeat of chest X-ray, plain films of the abdomen for LAG control, serum AFP and HCG. LAG was repeated at least once after disappearance of the contrast medium, usually 6 to 12 months after the first examination. CT of the abdomen was repeated every two visits. No patient was lost to follow-up which was closed on 30 June, 1985.

Results

Four of 75 patients were excluded because of either a second malignancy (3) or a post-operative course of chemotherapy (1). The latter patient had a false positive rise of AFP during the half-life kinetic study of the marker.

Of the remaining 71 patients, 50 (70.5%) are disease-free after a follow-up period of 12 to 46 months (median 27) and 21 (29.5%) have relapsed 2 to 36 months after orchiectomy (median 6 months). Three patients relapsed more than 1 year after orchiectomy: retroperitoneal metastases were diagnosed in two patients 17 and 36 months after orchiectomy and one patient had progressive AFP elevations after 22 months.

The site of the first relapse is illustrated in Table 1. The patient with a scrotal relapse had had a scrotal incision followed by radical inguinal surgery performed elsewhere. He developed lung metastases 5 months later. Two patients with lung metastases had further recurrences, one in the retroperitoneal nodes. So far, 12 of 71 patients (17%) have developed retroperitoneal lymph node metastases. The size and the interval free of metastases are detailed in Table 2. It is evident that lung metastases were diagnosed much earlier than retroperitoneal metastases. AFP and HCG were elevated in 14 of 21 patients (67%) with relapse. The elevation of serum tumour markers preceded the radiographic evidence of metastases in eight patients (38%).

Table 1 Relapse Pattern of Clinical Stage I NSGCT of Testis

Site of first relapse	*No.*	*(% of 71)*	*(% of 21)*
Scrotum	1	(1.4)	(4.8)
Retroperitoneal nodes only	8	(11.3)	(38.1)
Retroperitoneal and distant	3	(4.2)	(14.2)
Lung only	8	(11.3)	(38.1)
AFP only	1	(1.4)	(4.8)
Total	21	(29.6)	(100.0)

Table 2 Size and Interval Free of Metastases by Anatomical Sites

Metastatic sites	*< 2 cm*	*2-5 cm*	*> 5 cm*	*Free-interval (mos)*
Retroperitoneal nodes	1	7	4	7 (3-36)
Lung	10	1	—	3 (2-10)

Embryonal carcinoma, $T > 1$ categories, scrotal incisions and vascular invasion were associated with a higher relapse rate (Table 3). Pre-orchiectomy serum tumour markers AFP and HCG were of no prognostic value.

Table 3 Prognostic Factors in Stage I NSGCT of Testis

Prognostic feature	*Relapses/ cases*	*(%)*	*P value*
Teratocarcinoma	11/47	(23.4)	$=0.05$
Embryonal ca.	9/17	(52.9)	
T1	3/26	(11.5)	<0.05
T2, T3, T4a	9/20	(45.0)	
Inguinal surgery	11/53	(20.3)	<0.02
Scrotal incision	10/18	(55.5)	
No vascular invasion	4/15	(13.3)	$=0.10$
Vascular invasion	4/7	(57.1)	

The patient with the minimal retroperitoneal relapse refused therapy and died of widespread disease 7 months later, 11 months after orchiectomy. The other 20 patients became tumour-free with chemotherapy and/or surgery. Eighteen are in complete remission from 6 to 36 months (median 15) of starting salvage therapy. Of the two patients who had further relapses, one is disease-free 6 months after treatment of the third pulmonary relapse and the one who had a second relapse in the retroperitoneal nodes is alive with disease. The overall disease-free survival rate is 97% (69 of 71 patients).

Discussion

The occurrence of retroperitoneal metastases in our surveillance study was not significantly higher than expected after negative LAG and CT (Tesoro-Tess *et al.*, 1985), but lymph node metastases were usually diagnosed when larger than 2 cm. In one-third of cases they were first detected when larger than 5 cm. Furthermore, retroperitoneal metastases occurred late (Table 2) and the latest retroperitoneal relapse was diagnosed 36 months after orchiectomy.

We know of three other surveillance studies with a minimum follow-up of 2 years (Sogani *et al.*, 1985) or 1 year (Peckham, 1985; Schultz *et al.*, 1985). The relapse rate in the retroperitoneal nodes in these studies ranged from 15 to 20% and the latest relapse from these occurred in the retroperitoneal nodes 24, 31 and 34 months respectively after orchiectomy. Retroperitoneal metastases were <2 cm when first detected in only one of eight cases in the Memorial Hospital series and in approximately 50% of patients with retroperitoneal relapse in the Royal Marsden Hospital study.

It is evident that early detection of retroperitoneal metastases is not easy in the surveillance study. Patients must be followed up at regular intervals with repeat of LAG and CT scans for at least 3 years. Tumour markers AFP and HCG are not entirely reliable because they became elevated with relapse only in approximately 70% of cases (Peckham, 1985). The surveillance programme is therefore difficult and expensive and such close and prolonged follow-up may cause "psychological toxicity" in some patients. Furthermore, 2 of 45 patients in the Memorial Hospital series died of cancer.

On the other hand, retroperitoneal relapses are very rare after a properly executed RPLND. In our experience, retroperitoneal relapses did not occur in any of 102 patients with negative nodes (Pizzocaro *et al.*, 1985) and in only 2 of 100 patients with positive histology (Pizzocaro *et al.*, 1984; Pizzocaro and Monfardini, 1984). In both patients, relapses occurred outside the surgical field and both had extensive retroperitoneal disease. Surgical mortality was nil and the overall morbidity rate was 7%. It was severe in 3% of cases only. The major side effect of surgery was ejaculation failure, which occurred in about 70% of cases. However, only 13% of 61 consecutive patients who underwent unilateral RPLND for intra-operative stage I disease had permanent ejaculation failure (Pizzocaro *et al.*, 1985).

The follow-up of patients after RPLND is easy. Recently, 36 consecutive patients with clinical stage I NSGCT of the testis were submitted to RPLND alone and followed up with only repeat of chest X-ray and serum tumour markers at bi-monthly intervals (Pizzocaro, 1985). Eight patients (22%) had positive histology. After a minimum follow-up of at least 3 years, only four patients (11%) developed lung metastases. They were detected early and all have been cured with chemotherapy.

In conclusion, we suggest that unilateral RPLND may be preferable to surveillance in the management of clinical stage I NSGCT of the testis. Post-operative mortality is nil, morbidity is acceptable, ejaculation is lost in only a few patients, the follow-up is easier and risk factors for metastases can be studied (Klapp *et al.*, 1985; Pizzocaro, 1985). By comparison, surveillance may be preferred in those centres with facilities for close follow-up and study of risk factors for metastases. Both methods of management have equally good results (Peckham, 1985; Schultz *et al.*, 1985).

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The Authors

G. Pizzocaro, MD, Chief of Urologic Section, Department of Surgery.
F. Zanoni, MD, Senior Assistant
A. Milani, MB, Senior Assistant.
R. Salvioni, MD, Junior Assistant.
L. Piva, MD, Junior Assistant.

Requests for reprints to: G. Pizzocaro, Istituto Nazionale Tumori, via Venezian 1, 20133 Milano, Italy.

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Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours. Results of Management by Primary Chemotherapy

M. J. PECKHAM and W. F. HENDRY

Testicular Tumour Unit, Royal Marsden Hospital, Sutton

Summary—Between 1977 and 1984, 92 patients with clinical Stage II non-seminomatous germ-cell testicular tumours were treated by primary chemotherapy, with surgery reserved for the excision of persisting masses. Eighty patients (87%) are alive and disease-free: 96% for Stages IIA and IIB and 74% for Stage IIC. Of 43 Stage IIA, B and C patients treated with bleomycin, etoposide and cisplatin (BEP), 40 (93%) are disease-free. For the whole group there was a significant difference between the outcome of treatment in patients with retroperitoneal masses >8 cm in transverse diameter compared with those in whom masses were <8 cm, the disease-free rates being 54 and 97% respectively. Primary histology did not influence the outcome of treatment. However, whereas 51% of patients with teratocarcinoma had masses resected after chemotherapy, only 26% of embryonal carcinoma patients came to surgery. The results obtained in this series are as good as those obtained when lymph node dissection is employed as the initial form of treatment. The avoidance of surgery with preservation of ejaculatory function in 78% of Stage IIA and IIB patients argues in favour of an initially non-surgical approach to management.

Before the introduction a decade ago of effective chemotherapy for testicular tumours, Stage II disease was managed by radiotherapy or radical lymph node dissection. Approximately 80% of patients with small lymph node metastases were curable with radiotherapy, but the failure rate in patients with metastases >2 cm in diameter was high (Tyrell and Peckham, 1976). Similarly with surgery alone the relapse rate in patients with macroscopically positive nodes was approximately 50% (Staubitz *et al.*, 1973; Whitmore, 1979; Pizzocaro and Monfardini, 1984).

Since 1977 we have employed chemotherapy as primary treatment for clinical Stage II patients with surgical resection of residual masses after chemotherapy (Hendry *et al.*, 1981; Tait *et al.*, 1984). Between 1977 and 1981, post-chemotherapy radiotherapy was used on a selective basis (Duchesne and Peckham, 1984). In this report we describe our experience in 92 previously untreated clinical Stage II non-seminoma patients.

Patients and Methods

The 92 patients were treated between 1977 and 1984. The observation time since the beginning of chemotherapy ranged from 12 to 97 months with median observation times for Stage IIA, IIB, and IIC patients of 32, 36 and 65 months respectively (Table 1).

All patients were previously untreated by either radiotherapy or chemotherapy and had clinical Stage II disease (metastases confined to abdominal nodes). Stage II was subdivided into IIA (metastases <2 cm in diameter), IIB (metastases 2-5 cm) and IIC (metastases >5 cm) (Peckham, 1981).

Staging

After orchiectomy, patients were staged with chest

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Table 1 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Outcome of Treatment by Primary Chemotherapy in Relation to Stage. (Royal Marsden Hospital, 1977-1984)

	Disease-free	*Alive with disease*	*Dead from tumour*	*Dead from intercurrent disease*
IIA 22	20* (91%)	1	1	—
IIB 32	32† (100%)	—	—	—
IIC 38	28 (74%)	—	6	4
Total 92	80 (87%)	1	7	4

Observation times (months) IIA: 12-65 (median 32)
IIB: 12-82 (median 36)
IIC: 18-97 (median 65).

* One patient lost to follow-up at 18 months.

† One patient relapsed at 8 months and is disease-free 28 months after salvage treatment (methotrexate and radiotherapy).

X-ray, CT scans of abdomen and thorax, ultrasonic scans of liver and retroperitoneum, intravenous urography and lymphography. Serum concentrations of alphafetoprotein (AFP) and human chorionic gonadotrophin (HCG) were measured both initially and at each subsequent in-patient or clinic visit.

Histology

The histology was reviewed in all patients and classified into the following categories: malignant teratoma intermediate (teratocarcinoma), malignant teratoma undifferentiated (embryonal carcinoma), and malignant teratoma trophoblastic. In addition to these categories, seminomas with raised serum AFP levels were included in the study (3/92 patients).

Chemotherapy

Between 1976 and 1978, chemotherapy consisted of vinblastine and bleomycin (VB) (Samuels *et al.*, 1976), from 1978 to 1980 cisplatin, vinblastine and bleomycin (PVB) (Einhorn and Donohue, 1977) and between 1979 and 1984 bleomycin, etoposide and cisplatin (BEP) (Peckham *et al.*, 1983). Details of drug dosage, scheduling and toxicity have been published previously (Peckham *et al.*, 1979, 1981, 1983). In selected patients with small volume metastases bleomycin was omitted and etoposide and cisplatin (EP) employed (Peckham *et al.*, 1985a). Five patients received bleomycin only on day 2 (B_2EP) as part of a prospective Medical Research Council trial and two patients received carboplatin, etoposide and bleomycin (Peckham *et al.*, 1985b). One month after 4 cycles of chemotherapy, patients were reassessed by repeat CT scans and serum markers. Of the 22 Stage IIA patients, 20 had four cycles of chemotherapy and two had two cycles. Only one IIB patient had six cycles of chemotherapy; the remainder received four cycles. Of the 38 IIC patients, 33 had four cycles and five had six cycles of chemotherapy. Patients with residual masses after chemotherapy were considered for surgery as described elsewhere (Hendry *et al.*, 1981).

Results

Table 1 summarises the results of treatment. Of 92 patients, 80 (87%) are alive and disease-free, one is alive with disease, seven have died of tumour and four of complications (one post-operative death, one of renal failure, one of bleomycin lung damage and a fourth at 43 months of late radiation damage following abdominal irradiation after chemotherapy and surgery).

Of 54 Stage IIA and IIB patients, 52 (96%) are alive and disease-free. One Stage IIA relapse occurred in a B_2EP patient and one in a patient treated with EP chemotherapy which, as reported elsewhere, has been associated with an unacceptably high failure rate in patients with small metastases (Peckham *et al.*, 1985a). There was one IIB relapse at 3 months; this patient has been successfully re-treated with high dose ($3\,g/m^2$) methotrexate followed by radiotherapy and is disease-free 23 months after irradiation. In Stage IIC there were seven relapses, all within the first year after treatment. Six of this group have died and one is alive and disease-free 77 months after further chemotherapy. Of the nine relapsing Stage II patients, eight recurred within the abdomen and one patient developed lung metastases soon after excision of a residual abdominal mass of mature teratoma.

Table 2 shows the outcome of treatment by chemotherapy. Of 43 patients treated with BEP, 40 (93%) are alive and free from disease. The only two

Table 2 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours Managed by Primary Chemotherapy: Outcome of Treatment by Drug Regimen. (Royal Marsden Hospital, 1977-1984)

Chemotherapy regimen	*IIA*	*IIB*	*IIC*	*Total*
VB	—	—	2/4	2/4
PVB	3/3*	7/7	15/19	25/29 (86%)
BEP	10/10	19/19	11/14	40/43 (93%)
EP	4/5	4/4	—	8/9
B$_2$EP	3/4	1/1	—	4/5
JEB	—	1/1	0/1	1/2
Total	20/22	32/32	28/38	80/92 (87%)

* Disease-free/total treated.

relapses were both in Stage IIC patients. One patient died of bleomycin lung damage after six cycles of chemotherapy and a second patient, an elderly man, died of renal failure after ifosfamide was given as salvage chemotherapy following relapse after BEP. The results using PVB were slightly inferior, with 25/29 patients (86%) alive and disease-free.

Table 3 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Radiotherapy and/or Surgery after Chemotherapy. (Royal Marsden Hospital, 1977-1984)

Clinical stage	*Number of patients*	*Involved site radiotherapy after chemotherapy**	*Surgery after chemotherapy radiotherapy*
IIA	22	3 (14%)	4 (18%)
IIB	32	7 (22%)	8 (25%)
IIC	38	17 (45%)	22 (58%)
Total	92	27 (29%)	34 (37%)

* Discontinued in 1981.

Post-chemotherapy radiotherapy and/or surgery

As shown in Table 3, 27/92 patients (29%) had elective radiotherapy after chemotherapy and 34/92 (37%) had residual retroperitoneal masses excised. As expected, with increasing size of abdominal masses at presentation, the percentage of patients proceeding to surgery increased. For Stages IIA, IIB and IIC respectively, 18, 25 and 58% underwent laparotomy. Of the 54 Stage IIA and IIB patients only 12 (22%) came to surgery.

Size of retroperitoneal mass and outcome of treatment

Table 4 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Influence of Size of Abdominal Mass on Outcome of Chemotherapy. (Royal Marsden Hospital, 1977-1984)

Maximum diameter of abdominal metastases (cm)	*Number of patients*	*Alive and disease-free (%)*
<5	54	52 (96)
5-7	21	19 (90)
8-9	4	3 (75)
≥10	9	4 (49)

As shown in Table 4, of 88 patients where details of the maximum transverse diameter of the tumour could be obtained from CT scans, those with masses <8 cm showed a high probability of being cured (71/75: 97%); when masses were ≥8 cm in diameter the failure rate was higher, with only 7/13 patients (54%) alive and disease-free ($P < 0.05$).

Histology of primary tumour, complete remission rate and outcome of treatment

Table 5 shows the results of chemotherapy assessed in terms of complete remission (CR) rate 1 month after completion of the last cycle of treatment. The percentage of CR for embryonal carcinoma was significantly higher than for teratocarcinoma (43 and 23% respectively) ($P < 0.05$). This is not unexpected since teratocarcinoma primary tumours are associated with metastases where histological evidence of differentiation is seen and where after chemotherapy mature teratoma is a common finding (Tait *et al.*, 1984). This is shown in Table 6; of 20 teratocarcinoma patients coming to surgery, 16 (80%) had mature teratoma masses excised. Conversely, of 12 embryonal carcinoma patients who came to surgery, six (50%) showed fibrosis/necrosis in resected tissue. Table 5 also shows that the CR rate is influenced by substage for both teratocarcinoma and embryonal carcinoma.

In spite of the differences in complete remission rate, the disease-free rates for embryonal carcinoma and teratocarcinoma patients were comparable, with three tumour-related deaths in each histological subgroup. When substage and primary histology were examined in relation to the need for post-chemotherapy surgery, the percentage of patients proceeding to laparotomy increased with increasing tumour volume. Thus for embryonal carcinoma the percentages undergoing surgery after chemotherapy were 9, 17 and 50% for Stages IIA, IIB and IIC respectively. The comparable figures for teratocarcinoma were 33, 42 and 67%. Of 34 patients who came to surgery, 21 (62%)

Table 5 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Complete Response Rate One Month after Chemotherapy in Relation to Histology. (Royal Marsden Hospital, 1977-1984)

Stage	*Embryonal carcinoma (MTU)*	*Teratocarcinoma (MTI)*	*Trophoblastic teratoma (MTT)*	*Seminoma with AFP levels*
IIA	*9/12 (67%)	3/9 (33%)	1/1	—
IIB	8/18 (44%)	4/12 (33%)	0/2	—
IIC	3/16 (19%)	2/18 (11%)	1/1	0/3
Total	20/46 (43%)	9/39 (23%)	2/4	0/3

* = $\frac{\text{complete remission at restaging 1 month after chemotherapy}}{\text{total number of patients treated}}$

Table 6 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Influence of Primary Histology on Surgery after Chemotherapy and Histology of Resected Tissue. (Royal Marsden Hospital, 1977-1984)

Histology of primary tumour	*Total patients*	*Number with masses resected after chemotherapy*	*Histology of resected masses*		
			Fibrosis/ necrosis	*Mature teratoma*	*Cancer*
Embryonal carcinoma (MTU)	46	12 (20%)	6	4	2
Teratocarcinoma (MTI)	39	20 (51%)	1	16	3
Trophoblastic teratoma (MTT)	4	—	—	—	—
Seminoma AFP +	3	2	—	1	1

Table 7 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Outcome in Relation to Histology of Masses Resected after Chemotherapy. (Royal Marsden Hospital, 1977-1984)

Histology of resected tissue	*Number of patients*	*Alive disease-free*	*Alive with disease*	*Dead of tumour*	*Dead of intercurrent disease*
Fibrosis/necrosis	7	5	—	1	1
Mature teratoma	21	21	—	—	—
Malignant tissue	6	2	—	4	—

showed mature teratoma in the resected specimen. Six patients had residual malignant tissue and two of these are alive at 26 months and 41 months following further chemotherapy. Histology of resected masses and outcome of treatment are shown in Table 7.

Pre-chemotherapy serum marker status

Table 8 summarises serum AFP and HCG findings prior to chemotherapy. Of the 92 patients, 71 (77%) had raised levels of one or both markers.

Discussion

The major controversy in the management of clinical Stage II testicular non-seminoma centres on the role of lymph node dissection as a primary procedure. Unfortunately, there are few data allowing direct comparison between The Royal Marsden Hospital staging classification and outcome of surgery. Table 9 compares the outcome of node dissection in clinical Stage IIA and IIB patients managed by node dissection or by primary chemotherapy. In the surgical series 52% of patients required either immediate chemotherapy or chemotherapy at relapse. The eventual outcome in terms of percentage of disease-free survivors is closely similar. In the National Cancer Institute sponsored intergroup adjuvant chemotherapy study (Einhorn *et al.*, 1985), two cycles of platinum-containing chemotherapy successfully dealt with residual disease after node dissection. However, it is difficult to compare the patient population in the intergroup

Table 8 Clinical Stage II Non-seminomatous Germ Cell Testicular Tumours: Serum Marker Status Prior to Chemotherapy. (Royal Marsden Hospital, 1977-1984)

Stage	*Total number patients*	*Raised serum AFP and/or HCG levels prior to chemotherapy*	*Range of serum marker levels (median)*	
			AFP (ku/l)	*HCG (iu/l)*
IIA	22	16 (73%)	7-2500 (27)	29-2300 (194)
IIB	32	22 (69%)	7-4240 (246)	10-1790 (405)
IIC	38	33 (87%)	25-19000 (500)	4-1980 (96)

Table 9 Management by Primary Surgery or Chemotherapy for Clinical Stage IIA and IIB

Authors	*Number of patients*	*Number of patients undergoing radical node dissection*	*Number of patients receiving chemotherapy*	*Disease-free survivors*
Peckham *et al.* (1983)	54	—	54 (100%)	52 (96%)
Pizzocaro (pers. com.)	75	75	39 (52%)	74 (99%)

study directly with our experience in clinical Stage IIA and IIB patients since some of the node-positive patients in the adjuvant chemotherapy series would have had clinical Stage I disease before surgery.

It is generally agreed that bulky Stage II patients should be managed by primary chemotherapy since debulking surgery is not contributory (Javadpour *et al.*, 1982). For most clinical Stage IIA and IIB patients managed surgically, unilateral node dissection is inappropriate; hence interference with ejaculatory function is highly probable.

In the present study, 73% of clinical Stage IIA patients and 69% of Stage IIB patients had raised serum marker levels. In marker-negative patients care was taken to establish that nodal deposits were present either by performing sequential scans, lymphogram follow-up films or by CT-guided fine-needle aspiration biopsy.

It is clear that clinical Stages IIA and IIB constitute a highly favourable group of patients when managed by either surgery or primary chemotherapy. The choice between the two methods of treatment depends partly upon patterns of established practice and partly upon their relative toxicities. Surgery avoids chemotherapy in approximately 50% of patients unless adjuvant chemotherapy is employed, in which case, as discussed above, two cycles of chemotherapy have been shown to be effective. Whether two cycles of chemotherapy would be equally effective as primary management in clinical Stage II patients with small volume metastases remains to be established. Ejaculatory failure is a far from negligible complication of node dissection and the longer-term psychological morbidity of this complication remains unknown. This issue is particularly important, since recovery of spermatogenesis after chemotherapy appears to occur in approximately 90% of patients (Drury, unpublished data). Furthermore, there is no evidence that children fathered by men treated with chemotherapy are at increased risk of congenital malformation (Senturia *et al.*, 1985). The progressive move towards less toxic chemotherapy with the possible replacement of cisplatin with the non-nephrotoxic platinum analogue carboplatin (Peckham *et al.*, 1985b) is likely to make chemotherapy increasingly attractive as primary treatment in clinical Stage IIA and IIB patients.

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The Authors

M. J. Peckham, MD, MRCP, FRCR, Professor of Radiotherapy.

W. F. Hendry, ChM, FRCS, Consultant Urologist.

Requests for reprints to: M. J. Peckham, Testicular Tumour Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT.

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Lymphocyte Sub-populations in the Male Genital Tract

M. I. M. EL-DEMIRY, T. B. HARGREAVE, A. BUSUTTIL, K. JAMES, A. W. S. RITCHIE and G. D. CHISHOLM

University Department of Surgery/Urology and Department of Pathology, Western General Hospital, Edinburgh

Summary—A series of monoclonal antibodies that react with human lymphocyte subsets was used in an indirect immunoperoxidase technique to study representative blocks from normal human testis, epididymis, vas deferens, prostate and seminal vesicles. Biopsies of testis, epididymis and vas obtained during surgical procedures directed at the investigation and treatment of infertile males were also studied. In all normal tissues, apart from the peripheral testis where no lymphocytes were identified, T lymphocytes were the predominant cell type (Leu 4 +). These lymphocytes were largely of the suppressor/cytotoxic phenotype (Leu 2a +) and were more abundant in between the epithelial cells in the rete testis, epididymis, vas deferens, seminal vesicles and prostatic acini. Cells of the helper/inducer phenotype (Leu 3a +) were identified mainly within the interstitium of the epididymis and the prostate. B-lymphocytes (Leu 12 +) were few in number and were mainly in the stroma of the prostate. In each organ the ratio of the T-cell subsets was determined and changes in this ratio were observed in epididymal and vasal biopsies from some infertile males. Finally, in testis biopsies from infertile men, suppressor/cytotoxic T-cells were demonstrated between the germinal epithelium and the fibrous tunica of the seminiferous tubules and as focal aggregates in the interstitium.

Immunogenicity of sperm cells and their ability to induce specific auto- and iso-immunity were reported as early as the turn of this century (Metlanikoff, 1900). Autoimmunity as a cause of infertility in men was initially reported by Rumke in 1954.

B and T lymphocytes are required for the generation of immune responses. B-lymphocytes are responsible for the expression of the humoral immunity, the production of antibodies, while T-lymphocytes are the main effector cells of cell mediated immune reactions. Two distinct subsets of human peripheral T-cells have recently been characterised by monoclonal antibodies. They control both the type and intensity of cellular and humoral immune responses by acting as helper/inducer or suppressor/cytotoxic cells (Reinherz and Schlossman, 1980). Therefore, determination of the precise location of lymphocyte subset populations within the tissues of the male genital tract is of considerable importance in understanding the autoimmune infertility. In the present study we have demonstrated and characterised the lymphocytes in testis, epididymis, vas deferens, prostate and seminal vesicles using monoclonal antibodies to human lymphocytes in an immunoperoxidase technique.

Materials and Methods

Tissue

Specimens of normal human testis, epididymis, vas deferens, prostate and seminal vesicles were obtained from five multi-organ transplant donors. Specimens of the vas deferens were also obtained from vasectomy patients. Surgical biopsies of testis (10) and epididymis (5) were obtained from patients under investigation and treatment of infertility.

Tissues were frozen in liquid nitrogen within 1 to

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2 h of surgical removal and stored at −70°C until used. Several blocks were prepared from each tissue and 5 µm cryostat sections were cut from each block. Sections were air dried for 1 to 2 h under a hair dryer and kept at −20°C until used.

Antisera

These included the monoclonal antibodies* anti-Leu 4 which defines the entire population of T-lymphocytes, anti-Leu 3a which defines the helper/inducer T-cell subset, anti-Leu 2a which defines the suppressor/cytotoxic T-cell subset and anti-Leu 12 which defines B-lymphocytes. The specificities of these antibodies have previously been described (Engleman *et al.*, 1981; Ledbetter *et al.*, 1981).

Immunoperoxidase Technique

The indirect labelled antibody method was applied (Nakane and Pierce, 1966). Immediately before staining the frozen sections were fixed in acetone for 10 min, air dried and washed in 0.05 M, pH 7.6 Tris-HCl buffer saline (TBS). Serial sections from each block were overlayed with 60 µl of the appropriate dilutions of the monoclonal antibodies for 30 min. Negative control sections were treated with TBS only. As positive controls the monoclonal antibodies were applied to frozen sections of lymph nodes. Subsequently all sections were incubated with peroxidase conjugated rabbit anti-mouse immunoglobulin (Dakopatt A/S) for 30 min diluted 1/50 in TBS. All incubations were performed in moist chambers at room temperature. Between incubations, the sections were washed for 5 min in two changes of TBS. The final reaction was achieved by incubating the sections with 0.01% hydrogen peroxide and 0.05% diaminobenzidine tetrahydrochloride freshly prepared in TBS for 5 to 8 min. The sections were then rinsed in tap water and counter stained in Mayer's haematoxylin for 30 s, washed in tap water and mounted in Apathy's mounting medium.

Immunohistological Analysis and Scoring

The sections were examined by light microscopy using an X25 objective lens. The positively labelled cells were identified by their dark brown cell membrane staining and were scored within the epithelium, within the lamina propria and within the interstitial connective tissues. In almost every case the number of cells reacting with any individual monoclonal antibody was determined in 20 cross-sections using an eye-piece with a graticule. The total number of the mucosal epithelial cells in certain sections was also determined by counting cell nuclei. On the basis of these counts we were able to determine (a) the percentage of the mucosal epithelial cells—in certain tissues—which stained with individual monoclonal antibodies and (b) the ratio of the helper/inducer T-cells to the suppressor/cytotoxic T-cells in various compartments in each organ.

Results

The Testis

None of the antilymphocyte monoclonal antibodies used gave a detectable reaction with normal peripheral testis.

In marked contrast, T-lymphocytes (Leu 4+ cells) were always demonstrated in the rete testis with a predominance of cells of the suppressor/cytotoxic phenotype (Leu 2a+) (Table 1).

Table 1 Suppressor/Cytotoxic T-Lymphocytes (Leu 2a+) as a Percentage of the Total T-Cell Population (Leu 4+) within the Epithelium of the Male Genital Tract (Leu 2a+/Leu 4+)

Tissue	*% of T S/C*
Rete testis	61.0 (59.4-62.7)
Epididymis	
Head	80.7 (77.5-84.3)
Body	79.1 (72.4-84.1)
Tail	72.7 (62.6-80.3)
Vas deferens	65.9 (60.3-71.5)
Prostate	68.4 (52.1-84.7)
Seminal vesicles	62.0 (61.7-62.8)

While no lymphocytes were detected in the normal peripheral testis, T-lymphocytes were demonstrated in 10/10 testicular biopsies obtained from infertile patients. These T-lymphocytes were almost always of the suppressor/cytotoxic phenotypes (Leu 2a+). They were found in two locations. Isolated cells were noted between the fibrous tunica propria and the germinal epithelium of the seminiferous tubules. No cells were identified within the germinal epithelium. The other lymphocytes were arranged in small aggregates and follicles within the intertubular connective tissues (Fig. 1).

The Epididymis

In normal tissues no Leu 12+ cells (B-cells) were

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*These monoclonal antibodies were obtained from Becton Dickinson, Mechelen, Belgium.

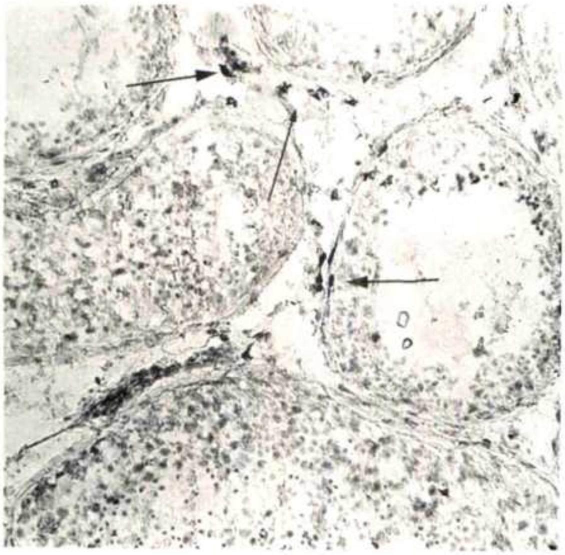

Fig. 1 Immunoperoxidase staining of a testicular biopsy from a sub-fertile patient with idiopathic oligozoospermia. Leu 2a + cells (suppressor/cytotoxic T-lymphocytes) are seen in the outer layer of the wall of the seminiferous tubules and in the interstitium. (Cryostat section, immunoperoxidase × 28).

seen. Leu 4+ cells (T-lymphocytes) were the predominant cell type. They were estimated to represent 12.7% of the mucosal cell population in the epithelium. Up to 77.9% of these T-lymphocytes were of the suppressor/cytotoxic phenotype (Leu 2a+) (Table 1, Fig. 2a). T-lymphocytes of the helper/inducer phenotype (Leu 3a+) were more abundant in the interstitium (Fig. 2b). Detailed results for the epididymis have been reported by El-Demiry *et al.* (1985).

The Vas Deferens

In the scrotal portion of the vas deferens, a T-lymphocyte population (Leu 4+) was demonstrated in between the epithelial cells and within the lamina propria. These T-lymphocytes constituted 25% of the epithelial cell population. Up to 66% of this T-cell population were suppressor/cytotoxic T-cells (Leu 2a+) (Fig. 3). However, the ratio of the suppressor/cytotoxic T-lymphocytes to the helper/inducer T-lymphocytes was very close to that in the epididymis (Table 2). This ratio was changed in surgical biopsies obtained from patients during vasectomy reversal operations where marked increases of helper/inducer T-cells (Leu 3a+) were noted.

The Ampulla of the Vas and Seminal Vesicles

In these sites, few T-lymphocytes were demonstrated and they were mainly of the suppressor/cytotoxic phenotype (Leu 2a+). They were located within the convoluted epithelial lining of both the ampulla of the vas and the seminal vesicles (Table 1).

The Prostate

No hyperplastic or inflammatory changes were seen in the specimens examined. The ducts and other acinar tissues were lined by columnar epithelium.

Lymphocytes were demonstrated within the epithelial lining, within the lumina of the ducts in proximity to the corpora amylacea and in immediately periductal connective tissues as well as in the intertubular connective tissue septa (Fig. 4a). The intra-epithelial lymphocytes were almost all T-lymphocytes and largely of suppressor/cytotoxic phenotype (Table 1). They tended to lie close to the basement membrane but very occasionally some cells appeared further up, in between the epithelial cells towards the lumen (Fig. 4b).

The interstitial positively labelled cells were more abundant and were mainly T-cells of the helper/inducer phenotype. They tended to be arranged in clumps rather than singly. Similarly, there was a tendency to aggregation of lymphocytes within the interlobar septa of connective tissue; B-cell aggregations (Leu 12+) were also seen in the interstitial tissues.

Discussion

Lymphocytes have been reported in the epithelium of the intestinal tract (Ferguson, 1977; Selby *et al.*, 1981), the respiratory tract (Beinenstock *et al.*, 1973) and the reproductive tract (Reid and Cleland, 1957; Hamilton, 1972; Hoffer *et al.*, 1973; Dym and Romrell, 1975). It has been suggested that these lymphocytes are more likely to be present in every mucosal epithelial layer forming a common mucosal immunological system (Bienenstock *et al.*, 1980). Ritchie *et al.* (1984) first used monoclonal antibodies to study lymphocyte distribution within the epididymis and the colour illustrations in that report clearly illustrate the striking results obtained by the immunoperoxidase technique.

In this study we have demonstrated and characterised lymphocytes along the length of the human male genital tract. Lymphocytes were almost always T-cells and they tended to be concentrated in large numbers in the epididymis, the vas deferens and the prostate respectively. They were few in

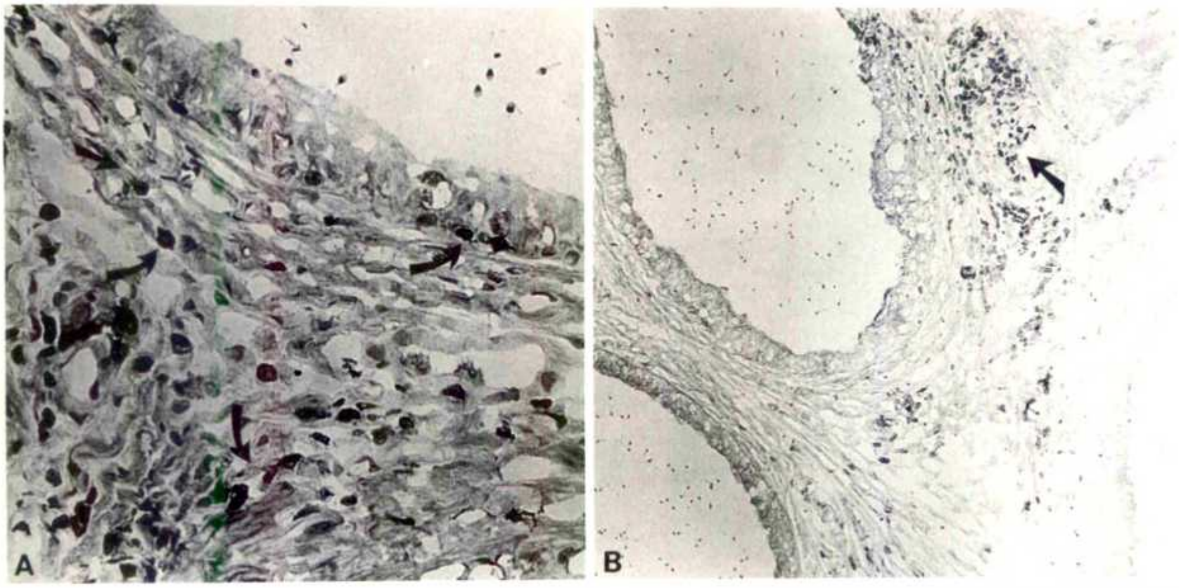

Fig. 2 (A) Human epididymis stained with anti-Leu 4 (Pan T-cells marker). T-lymphocytes are seen in the epithelium, lamina propria and in the interstitium. (Cryostat sections, immunoperoxidase × 64). (B) Human epididymis stained with anti-Leu 3a (which defines helper/inducer T-lymphocytes). These T H/Ind lymphocytes are more abundant in the interstitium. (Cryostat sections, immunoperoxidase × 25).

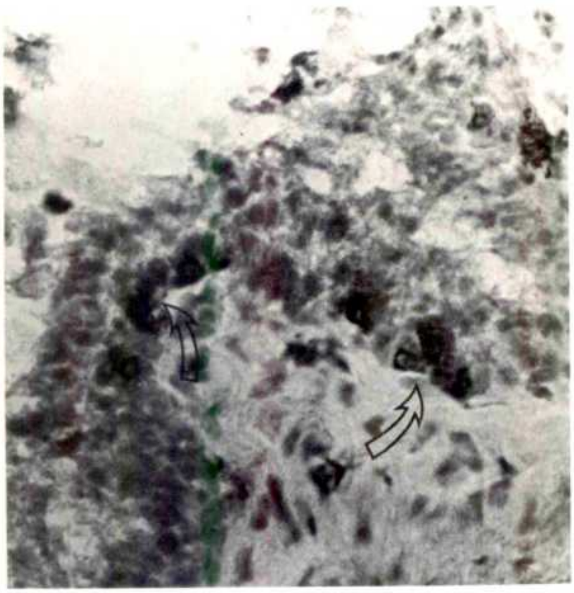

Fig. 3 Leu 2a + cells (suppressor/cytotoxic T-lymphocytes) in the lining epithelium of the human vas deferens. (Cryostat section, immunoperoxidase × 77).

Table 2 Average Ratio of Suppressor/Cytotoxic T-Lymphocytes to Helper/Inducer T-Lymphocytes in Normal Male Genital Tract

Tissue	*Intra-epithelial*	*Lamina propria*	*Interstitial tissue*
Rete testis	2.1 (1.8-2.3)	—	0.6 (0.5-0.7)
Epididymis			
Head	4.1 (3.5-5.5)	1.4 (1.1-2.3)	0.5 (0.39-0.69)
Body	3.0 (2.5-3.5)	1.3 (1.0-2.3)	0.6 (0.35-0.74)
Tail	2.4 (2.2-2.8)	1.7 (1.6-2.3)	0.4 (0.37-0.51)
Vas deferens	1.8 (1.2-2.4)	1.6 (1.2-1.9)	
Prostate	2.6 (2.4-2.8)	—	3.9 (3.2-4.7)
Seminal vesicles	1.2 (1.19-1.23)	1.2 (1.1-1.3)	—

(Ratio in peripheral blood is 0.5)

number in the rete testis, ampulla of the vas and seminal vesicles. B-lymphocytes were demonstrated only in the stroma of the prostate.

T-lymphocytes exhibited a compartmentalised distribution. Within the epithelium, lymphocytes of the suppressor/cytotoxic phenotype were the major component. This was observed at all levels of the genital tract (Table 1). Suppressor/cytotoxic T-cells were also preponderant in the lamina propria of the epididymis, vas deferens and seminal vesicles. In contrast, the helper/inducer T-lympho-

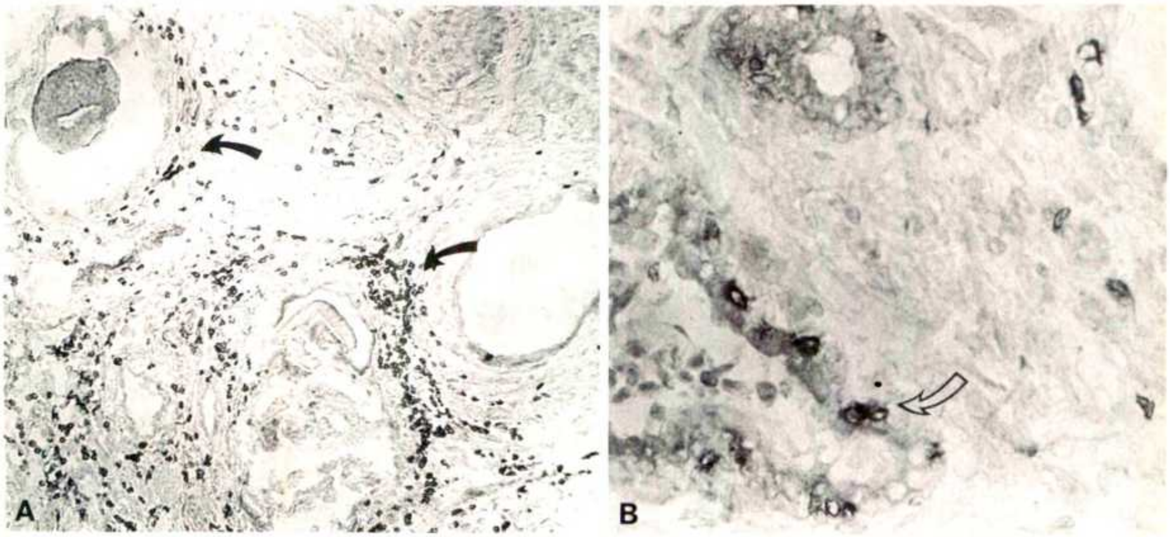

Fig. 4 (A) Leu 4+ cells (T-lymphocytes) in normal human prostate are seen in the lining epithelium of the prostatic acini, in lumina ducts and in the interstitium. (Immunoperoxidase ×40). (B) Leu 2a+ cells (suppressor/cytotoxic T-lymphocytes in the lining epithelium of prostatic acini. (Immunoperoxidase ×65).

cytes were more abundant in the interstitial connective tissues (Table 2). It is most likely that the predominant suppressor/cytotoxic T-cells in the epithelial lining of male genital tract function form a major immunological barrier which normally prevents the development of autohumoral or cellular immune responses to sperm antigens.

The pattern of distribution of this suppressor barrier is consistent with the functional properties of each organ, namely the absence of the lymphocytes from the normal peripheral testis, where there is an anatomical blood-testis barrier formed by the Sertoli cells and which appears only at puberty (Kormano, 1967; Vitale *et al.*, 1973; Setchell, 1980). Freund and Davis (1969) reported that 60 to 70% of the spermatozoa within a normal ejaculate come from the epididymis and proximal part of the vas deferens. The testicular fluid is also absorbed in the epididymis. Since it is well established that human sperm are immunogenic, the absorption of the products of sperm breakdown in the epididymis represents an enormous immunogenic stimulation which will lead to initiation of immune responses. But it seems that under the conditions of a healthy genital tract, this sperm-immunogenic stimulation can be easily handled by the immunological suppressor barrier ($T_{s/c}$) in the lining epithelium of the epididymis and to a certain extent in the vas deferens. This may also explain why the suppressor/cytotoxic T-cells are more abundant in the epididymis than the rest of the genital tract. The occurrence of sperm granuloma, testicular degeneration and the development of autoimmunity post-vasectomy and post-obstruction may illustrate the importance of the vas deferens and its epithelial suppressor barrier in the normal immune homeostasis of the male genital tract.

A potential consequence of this immunological suppressor barrier in the prostate is that infections and inflammations are commonly encountered in young men. Inflammation may result in occlusion of the ejaculatory duct and absorption of prostatic and sperm antigens. The demonstration of B-lymphocytes in the interstitial connective tissues of the prostate may account for the source and level of local secretion of immunoglobulins.

The finding that the epithelium of seminal vesicles contains few suppressor T-cells is also consistent with its function. The seminal vesicles are not a storage depot for spermatozoa and the secretions of the seminal vesicles are only in contact with the spermatozoa at the moment of ejaculation (Clavert *et al.*, 1985), *i.e.* there is little or no absorption of sperm antigen.

In conclusion, lymphocyte subpopulations were normally demonstrated in rete testis, epididymis, vas deferens, prostate and seminal vesicles, with a specific pattern of distribution in the epithelium, lamina propria and the interstitium. T-lymphocyte of suppressor/cytotoxic phenotype were found to constitute the larger part of the T-cell population along the epithelial lining of the genital tract organs (Table 2). The ratio of $T_{s/c}$ to $T_{H/Ind}$ was consistent in all of the specimens examined from each organ. Changes in this ratio were noted in clinical specimens but the true significance of this finding must await study of a larger number of abnormal specimens from patients with defined clinical problems.

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The Authors

M. I. M. El-Demiry, MB,BCh(Cairo), MSc(Urol Cairo), Senior Resident in Urology, Police Hospital, Cairo, Egypt. Honorary Registrar, University Department of Surgery/Urology.

T. B. Hargreave, MS, FRCS, FRCSE, Senior Lecturer and Consultant Urologist, University Department of Surgery/Urology.

A. Busuttil, MD, MRCPath, Consultant Pathologist, Western General Hospital.

K. James, DSc, FRCPath, FRSE, Reader in Surgery, University of Edinburgh.

A. W. S. Ritchie, MD, FRCSE, Senior Registrar, University Department of Surgery/Urology.

G. D. Chisholm, ChM, FRCS, FRCSE, Professor of Surgery and Consultant Urologist, Western General Hospital.

Requests for reprints to: M. I. M. El-Demiry, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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True Hermaphroditism. A Review of 41 Cases with Observations on Testicular Histology and Function

I. A. AARONSON

Department of Paediatric Urology, Red Cross War Memorial Children's Hospital, Cape Town, Republic of South Africa

Summary—Thirty-six children and five adults with true hermaphroditism have been reviewed. Twenty-five were raised as males and 16 as females. Those assigned as males had all ovarian tissue excised, leaving either a single testis or the testicular portion of one or both ovotestes. Post-operative testicular function was studied in 15 males. Basal testosterone levels were low in all four post-pubertal patients. Eleven children had plasma testosterone measured before and after stimulation with HCG. Response was poor in eight and normal in only three. Although social factors in South Africa usually result in true hermaphrodites being raised as males, the functional outcome of this decision is often disappointing.

True hermaphroditism is a rare cause of intersexuality in Western Europe and North America, but on the African continent it is among the most common. This report describes the clinical and cytogenetic features, gonadal histology and management of 41 patients seen at the University of Cape Town Teaching Hospitals during the past 18 years. We also report the post-operative testosterone output among 15 patients raised as males who retained either a single testis or the testicular part of one or both ovotestes.

Patients and Methods

This series comprised 36 children whose ages ranged from 2 weeks to 16 years, and five adults. The oldest, a 52-year-old woman who was the mother of nine children, has been reported previously (Tiltman and Sweerts, 1982). Twenty-nine were black and nearly all came from the traditional tribal areas of South Africa. Eleven were of mixed race and only one was white. There were no familial cases.

The karyotype was determined in all patients by examination of a minimum of 40 peripheral blood lymphocytes using standard incubation and photographic techniques. Thirteen also had pudendal skin, ovarian and testicular tissue examined. H-Y antigen and Y gene probe studies were not available. Genitography was carried out employing one of several methods previously described (Aaronson and Cremin, 1984). Ultrasound of the pelvic organs was carried out with an ATL MK100 real-time machine with a 5 mHz or 7 mHz transducer using the full bladder as an acoustic window.

The diagnosis in all cases depended upon the histological demonstration in the same patient of both testicular and ovarian tissue, the latter always containing at least one well formed follicle. Gonadal tissue and duct structures inappropriate to the sex of rearing were removed at laparotomy at the time of diagnosis after histological confirmation by frozen section. When the gonad was an ovotestis the appropriate portion was conserved whenever possible. All testicular tissue was brought down into the scrotum.

Post-operatively, plasma testosterone levels were measured by standard ether extraction and radioimmunoassay in four adults and 11 children raised as males who retained either a whole testis or part of one or both ovotestes. Basal values were

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obtained in the adults, whilst in children testosterone output was also measured following injection of HCG 1500 units/m^{2}SA given on days 1, 3 and 5, with sampling on day 6. These studies were carried out at least 4 weeks after surgery to allow the gonads to recover.

Results

Phenotype

The appearance of the genitalia ranged from near-normal female with mild clitoral hypertrophy, to male with a perineal hypospadias and well developed scrotal sacs each containing a fully descended gonad. Mostly, however, the genitalia were ambiguous, although tending towards male. Asymmetry of the labioscrotal folds was common, with the right nearly always the better developed. A gonad was also often palpable on this side.

Among the four adult males, three sought attention because of gynaecomastia and one because of cyclical haematuria. All claimed to have erections and one regular sexual intercourse with ejaculation.

Karyotype

All 41 patients were found to have a 46 XX lymphocyte karyotype. Among the 13 whose pudendal skin, ovarian and testicular tissue were also examined, all cells showed 46 XX with no evidence of mosaicism.

Genitogram and ultrasound

A vagina was demonstrated by genitography in 29 of 34 patients, whilst in another 4 it was shown by vaginography following endoscopic cannulation. The vagina was usually capacious and opened into the urethra below the pelvic floor even when the external genitalia were well masculinised. A uterus was also usually filled, although it was generally a rudimentary structure and only rarely did the cervix form a filling defect in the vaginal vault. A Fallopian tube was sometimes also filled, more often on the left side.

The four most recent patients have also been studied by ultrasound. A rudimentary uterus was demonstrated in three. In one infant both intra-abdominal gonads were identified but we were uncertain of their nature.

The gonads

The commonest findings were bilateral ovotestes or an ovary and a contralateral ovotestis (Table 1).

Table 1 Distribution of Gonadal Tissue in 41 True Hermaphrodites

Right	*Number*	*Left*
Ovotestis	16	Ovotestis
Ovotestis	12	Ovary
Testis	6	Ovary
Testis	5	Ovotestis
Ovary	2	Ovotestis

With only two exceptions, the right gonad was either predominantly or entirely testicular in nature. Ovotestes usually showed a clear demarcation between the ovarian and testicular portions, the former being firm, yellowish and gritty to the knife, whilst the latter was usually soft and pink. Histologically, the plane between the two components was also usually sharply defined. There were, however, three cases in which the ovarian tissue was confined to one or more small nodules in the hilum of an otherwise unremarkable testis, whilst in one case the gonad, which resembled a normal testis to the naked eye, was found histologically to consist of an admixture of ovarian follicles and testicular tubules diffusely distributed throughout a fibrous stroma.

The histological appearance of all ovarian tissue was normal, although the number of follicles varied quite widely. By contrast, testicular tissue from whole testes and ovotestes showed tubular atrophy and an increase in interstitial tissue in 18 of the 30 patients whose slides were available for review. These changes tended to be more pronounced in intra-abdominal ovotestes but could also be striking in fully descended testes (Fig. 1). The age of the patient at the time of biopsy also appeared to be important, for degenerative changes were usually absent or mild within the first year of life. However, two infants whose testicular tissue appeared unremarkable on light microscopy showed early germ cell degeneration on electron microscopy in the form of cytoplasmic vacuolation (Fig. 2). Leydig cells were unremarkable.

Management

Twenty-five patients were assigned as males and 16 as females. Among the latter were six initially thought to be male by their mothers who were reassigned on the grounds of a borderline phallus and a capacious vagina. However, there was usually strong family pressure among black parents to retain the child in the male role and this wish has generally been respected when the size of the phallus permitted a choice.

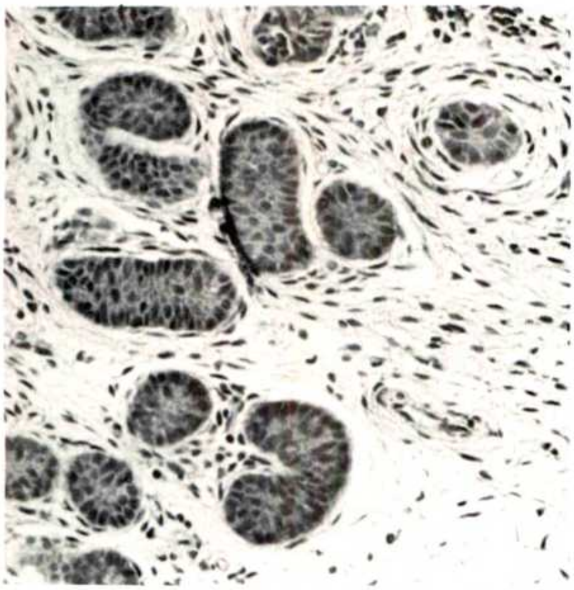

Fig. 1 Photomicrograph of the testis of a 4-year-old true hermaphrodite. Note the sparse immature tubules and abundant interstitial fibrous tissue. (Haematoxylin and eosin. Original magnification × 50).

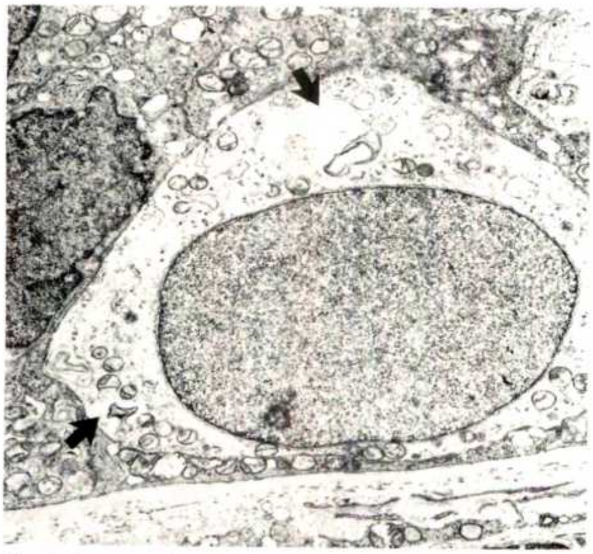

Fig. 2 Electron photomicrograph of a testicular biopsy of a 2-year-old true hermaphrodite showing a germ cell with cytoplasmic vacuoles (arrows). (Original magnification × 7840).

Among those raised as males, 11 retained testes which usually required orchiopexy. Fourteen patients had one predominantly testicular ovotestis, but in three of these the anatomy was unfavourable and it was removed. Ovarian tissue was excised in the remaining 11 and the testicular portion brought down into the scrotum. In three cases this was done on the artery to the vas with division of the gonadal vessels. Post-operatively, two were impalpable and one had retracted to the scrotal neck, but eight felt like normal testes. The uterus together with the Fallopian tubes was removed at the time of diagnosis but the vagina was resected only as far as could be conveniently reached. We are not aware of any child who has subsequently suffered any symptoms from the retained vaginal stump. Chordee correction and hypospadias repair were nearly always carried out as staged procedures with a satisfactory outcome.

Among girls, simple clitoral recession was generally cosmetically inadequate and most required excision of the central portion of the corpora with preservation of the neurovascular bundles together with partial excision of the glans. A very low lying vagina was usually exteriorised at the same time by a simple cut back but when more than a few millimetres above the skin, a U-flap vaginoplasty was carried out towards puberty. Post-operative vaginal dilatations were usually required for several months.

Post-operative endocrine studies

Plasma testosterone concentration was measured in four adult males who retained one testis and 11 children who retained the testicular component of one or both ovotestes (Fig. 3). All four adults had resting testosterone concentrations below those anticipated for normal males (N.R. 10-35 nmol/l). Among the 11 children, basal testosterone concentrations were below 2 nmol/l in all but one case, an infant of 6 weeks. Following HCG stimulation, plasma testosterone failed to reach anticipated levels in all but three children. There was no clear relationship between testosterone output and the original nature and position of the gonad, its post-operative size and consistency, or histological appearance.

Discussion

True hermaphroditism is the commonest cause of intersexuality seen at this hospital (Table 2) but the true incidence of the various disorders in South Africa is difficult to determine because of referral patterns, the imprecise use of the term male pseudohermaphrodite, and the probability that many infants with congenital adrenal hyperplasia die without the diagnosis ever being established.

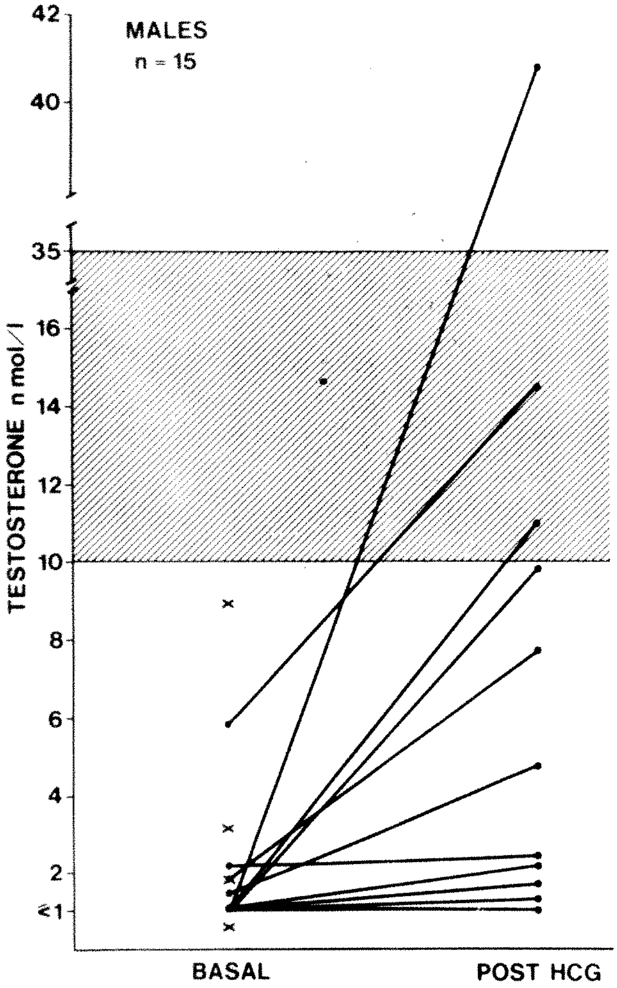

Fig. 3 Post-operative testosterone concentrations in true hermaphrodites raised as males. x = adults. ● = Children. Hatched area = Normal range for adult males.

Table 2 Causes of Intersexuality Among 75 Children Seen over a 10-year Period

Disorder	*Number*
True hermaphrodite	27
Male pseudohermaphrodite	23
Female pseudohermaphrodite	21
Gonadal dysgenesis	4

There are striking differences in the karyotype of true hermaphrodites in different regions of the world. In Southern Africa by far the commonest finding is 46XX (van Niekerk, 1974). Among our own cases all 41 were 46XX and none of the 13 patients in whom multiple tissues were examined showed any mosaicism. By contrast, mosaicism is seen in up to 50% of cases in Europe (Nihoul-Fékété *et al.*, 1984), usually with a 46XX/46XY or 47XXY line. In Japan the commonest karyotype is 46XY (Tazaki *et al.*, 1964). The reason for these differences is unknown.

Although the histological appearance of ovarian tissue in true hermaphrodites is nearly always normal and several pregnancies have been reported, testicular tissue is usually immature and spermatogenesis rare (van Niekerk, 1981). Among our patients, testicular biopsies taken in the first few months of life were generally normal, but with increasing age there was little evidence of tubular maturation and an increase in the amount of interstitial fibrous tissue. Although these changes are similar to those found in simple cryptorchidism, they were seen in fully descended testes as well as in intra-abdominal ovotestes. The degenerative changes we observed within the sparse germ cells on electron microscopy were also similar to those found in cryptorchidism (Cotelli *et al.*, 1980) and probably preceded the changes recognisable under the light microscope.

The reason, however, for the degeneration of testicular tissue in true hermaphrodites remains a matter for speculation (Donahoe *et al.*, 1978).

There is very little published data concerning *in vivo* testosterone production in true hermaphrodites either before surgery (Ghandchi *et al.*, 1979; Roy *et al.*, 1980; Berkovitz *et al.*, 1982), or after (Nihoul-Fékété *et al.*, 1984). Clinically, most untreated males have shown some virilisation at puberty, but the extent to which this is modified by the excision of ovarian tissue is unknown. None of our patients treated by partial gonadectomy has yet reached puberty, but their response to HCG stimulation was generally disappointing. Among our three children with a satisfactory response, one was only 6 weeks old, an age when plasma testosterone concentration is normally high (Forest *et al.*, 1973). The second had two ovotestes from which small caps of ovarian tissue were excised. The third retained approximately two-thirds of an ovotestis. A poor response could possibly be attributed to vascular damage in only two of the remainder in which the gonad became impalpable. The six other poor responders had a scrotal gonad which was easily palpable and felt like a normal or near normal testis.

Although the technical feasibility of preserving the testicular portion of ovotestes has been demonstrated, the functional value of such tissue or indeed of whole testes in true hermaphrodites is often disappointing. Although social pressures usually favour male as the sex of rearing, the need for supplementary endocrine replacement at puberty must be anticipated.

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The Author

I. A. Aaronson, FRCS, Consultant Urologist and Head of Department of Paediatric Urology, Institute of Child Health, University of Cape Town and Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town 7700, Republic of South Africa.

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Why Does Vasectomy Reversal Fail?

M. G. ROYLE and W. F. HENDRY

Departments of Urology, Royal Sussex County Hospital, Brighton and St Bartholomew's Hospital, London

Summary—The scrotum was explored in 32 patients who had vasectomy reversal which failed to restore their fertility. Twenty-three patients were azoospermic and nine had severe or persistent oligozoospermia. Amongst the 23 azoospermic cases, the vasa were found to be blocked in 12; following repeat vaso-vasostomy, normal sperm counts were produced in 10 patients; 8 of these patients followed up for 6 months or more successfully impregnated their wives. In four cases there was a secondary epididymal block: following epididymo-vasostomy, three of four patients obtained normal sperm counts and two wives became pregnant. In seven patients there was a very high antisperm antibody titre (>1024 by tray agglutination test) and despite reparative surgery and prednisolone therapy, no pregnancies were obtained. The overall pregnancy rate for this group was 7 of 19 (37%).

Amongst nine oligozoospermic cases, unilateral obstruction was found in eight. The block was found in the vas in five and in the epididymis in two, and in two there were very high antisperm antibody titres. After reconstructive surgery, four patients had normal sperm counts and one pregnancy has been obtained.

Vasectomy reversal successfully returns spermatozoa to the ejaculate in 70 to 90% of cases and 40 to 60% of wives become pregnant (Cos *et al.*, 1983). It is not entirely clear why the remainder fail to regain their fertility, although it is known that sperm granuloma formation at the site of the anastomosis can sometimes cause recurrent obstruction (Silber, 1977) and that rupture of the tubules in the epididymis can cause a secondary block at epididymal level (Silber, 1979). It is also known that vasectomy provokes antisperm antibody formation and although in most patients this does not impair fertility, the development of high titres of antisperm antibodies (512 or more) does lead to significant impairment of fertility (Parslow *et al.*, 1983). Finally, it is possible that the function of the testicles may deteriorate following vasectomy and so testicular failure or loss of spermatogenesis is a theoretical cause of failure of vasectomy reversal.

In order to clarify the problem, we analysed 32 patients who had vasectomy reversal which failed to restore their fertility. We re-explored the scrotum, defined the cause of the problems as far as possible, and carried out corrective surgery.

Patients and Methods

Twenty-three patients had no spermatozoa in the ejaculate at all, and nine had severe persistent oligozoospermia with sperm counts <10 m/ml, generally <1 or 2 m/ml. The age range of the patients was 26 to 54 years (average 39). Vasectomy had been done between 4 and 17 years previously (average 8). One to 11 years (average 2.5) had elapsed since the previous vasectomy reversal.

The scrotum was opened by either midline or bilateral oblique incisions. The tunica vaginalis was opened on both sides and the epididymes were inspected to see whether they contained distended tubules. If no distension was seen, a testicular biopsy was taken and nothing further was done on that side. If, however, the epididymis showed distended tubules, the vas was located and incised immediately on the testicular side of the previous

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

anastomosis. If clear or milky fluid ran out, this was taken as evidence of obstruction at the site of the previous anastomosis and the anastomosis was re-done by an overlapped side-to-side technique, using continuous 6/0 prolene (Fig. 1). If, on the other hand, no fluid ran out at this point, this was taken as evidence of obstruction closer to the testicle. Patency of the previous anastomosis was demonstrated whenever possible by passage of a nylon splint or injection of a little saline through a size 2F Porges tube inserted into the vas. Accordingly, epididymo-vasostomy was done (Fig. 2). The epididymis was freed from the body of the testicle and transected. Repeated transection of the epididymis was done until a good flow of milky fluid was obtained. End-to-side epididymo-vasostomy was then carried out, using a continuous 6/0 prolene stitch. The anastomosis was done either below or above the previous vaso-vasostomy, depending on the height at which the original vasectomy had been done. Whenever possible the fluid exuding from the cut end of the vas or the epididymis was examined microscopically for the presence of spermatozoa. The transected part of the epididymis was sent for histological examination.

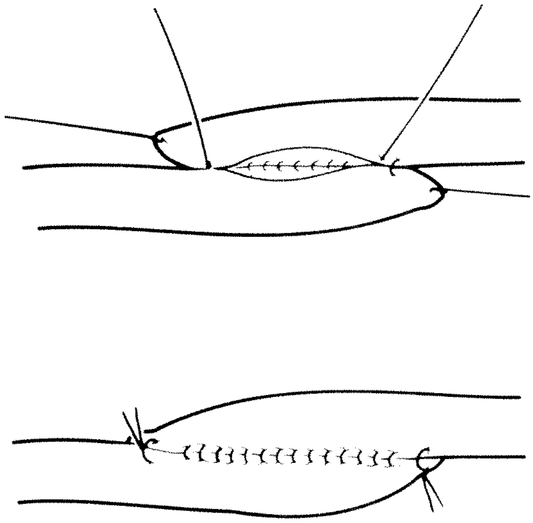

Fig. 1 Overlapped side-to-side anastomosis between the vasa, using continuous 6/0 prolene. Note the additional tension-relieving stitches at each end of the anastomosis.

Antisperm antibodies were tested in all cases by the tray agglutination test (Friberg, 1974).

Results

The results in 23 patients who were azoospermic prior to reconstructive surgery are shown in Table 1. In the first category were 12 patients in whom the anastomosis of the vasa had become blocked. Following repeat vaso-vasostomy by the technique described, spermatozoa were restored to the ejaculate in 10 patients; the wife of a further patient became pregnant before a sperm count had been done. Of eight patients followed up for 6 months or more, five (62%) impregnated their female partners.

In the second category (patients with epididymal blocks which were treated by epididymo-vasostomy), three of four patients regained satisfactory sperm counts and two wives became pregnant.

In the third group, comprising patients with very high antisperm antibody titres of 1024 or more, appropriate surgery and prednisolone treatment led to reasonable sperm counts in six patients (>20 m/ml in 3), but none of the wives became pregnant.

The overall pregnancy rate for this group was 37%.

We explored nine men with persistently poor sperm counts following previous vasectomy reversal, and the results are shown in Table 2. A blockage was found in the vas on one side, although at least partial patency had obviously been restored on the other side. The cases fell into the same categories as before, except that in eight of the nine cases only one side remained blocked. Corrective surgery resulted in improved sperm counts and one pregnancy has been obtained. In this particular case the patient had a rather poor testicle on one side which had been successfully reconnected, but was putting out less than 1 million spermatozoa per ml. Following reconnection of the contralateral normal testicle, the sperm count returned to normal and his wife has recently been delivered of a normal baby.

Discussion

There appear to be four distinct causes of failure of vasectomy reversal. The commonest by far, which should be anticipated in about one-half of these patients, is due to stenosis or blockage of the previous vaso-vasostomy. It is known that spermatozoa have a tendency to leak out of the anastomosis when vaso-vasostomy is done, and these may produce local granuloma formation. Hagan and Coffey (1977) showed that this appeared to be an important cause of failure. In 1977, Silber showed that excellent results could be obtained by repeating the vaso-vasostomy, using an extremely careful technique. We favour our method of vaso-vasostomy, using an overlapped

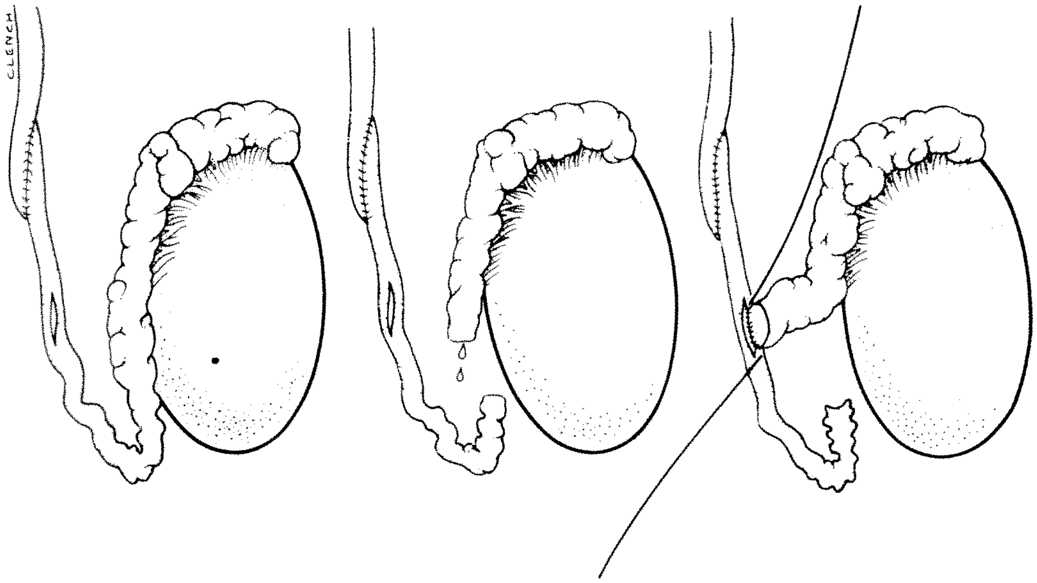

Fig. 2 Epididymo-vasostomy. The epididymis is mobilised off the body of the testicle and transected. Serial transection of the epididymis continues until a good flow of milky fluid is obtained from the epididymis. It is then anastomosed to the vas either above or below the previous vaso-vasostomy, depending on the height of the previous vasectomy and the patency or otherwise of the previous vaso-vasostomy.

Table 1 Results in 23 Azoospermic Patients

			Follow-up sperm counts			
Category	*Treatment*	*No.*	*0*	*<20*	*⩾20*	*Pregnancies**
1. Blocked vas	Repeat vas-vas	12	1	3	7	5/8 (62%)
2. Epididymal block	Ep-vas	4	1		3	2/4 (50%)
3. Antisperm antibodies (⩾1024)	Surgery + prednisolone	7	1	3	3	0/7
						7/19 (37%)

(* Trying for 6 months or more.)

Table 2 Results in 9 Oligozoospermic Patients

			Follow-up sperm counts		
Category	*Treatment*	*No.*	*0*	*<20*	*⩾20*
1. Blocked vas	Repeat vas-vas	5		1	4*
2. Epididymal block	Ep-vas	2		2	
3. Antisperm antibodies (⩾1024)	Surgery + prednisolone	2		1	
4. Testicular failure	None	½			

* 1 Pregnancy.

side-to-side anastomosis with continuous 6/0 prolene, which offers considerable advantages. Not only is a large opening obtained between the two parts of the vas, but the use of a continuous prolene suture produces a water-tight anastomosis which discourages the leakage of spermatozoa and hence reduces the tendency towards granuloma formation. Furthermore, the side-to-side technique eliminates any technical difficulties due to differences in the calibre of either end of the vas. As may be seen from the excellent results in terms of restoration of normal sperm count, and the incidence of pregnancy in the wives, the success rate in this group is equivalent to that obtained on first doing a vasovasostomy.

The cause of epididymal blockage is presumably back pressure from the site of the vasectomy, leading to rupture of epididymal tubules with local sperm granuloma formation within the epididymis. Histological examination of a section of epididymis removed at the time of epididymo-vasostomy will often demonstrate rupture of an epididymal tubule and surrounding sperm granuloma formation, which leads to the secondary blockage in the epididymis upstream of the original site of the vasectomy. Silber (1984) has described the technique for mobilising the epididymis and anastomosing it to the vas. We have confirmed that excellent results can be obtained following epididymo-vasostomy in these cases, although restoration of normal sperm count generally takes longer than following vasovasostomy.

The problem of the patient who develops a very high antisperm antibody response to his vasectomy continues to defy successful treatment. In previous studies (Parslow *et al.*, 1983) we showed that pregnancy was possible despite high antisperm antibody titres, but we have defined a small subpopulation in whom, despite re-exploration of the scrotum and prednisolone therapy, restoration of fertility does not seem to be possible, apparently due to the immunological response to the spermatozoa. This problem continues to present a significant therapeutic challenge.

Finally, spermatogenesis may have ceased. Our studies confirm the previous observations of Bagshaw *et al.* (1980), who showed by testicular biopsy studies that significant impairment of spermatogenesis following vasectomy was in fact extremely uncommon. Nevertheless, the possibility should be considered amongst these patients, many of whom are entering middle life at the time that this surgery is carried out.

It is difficult to estimate how many patients wish to have their vasectomies reversed, but a conservative estimate suggests that 1 or 2% of patients do so for reasons that are generally good and entirely understandable. Howard (1982) pointed out that many men undergo vasectomy at a time of severe emotional disturbance or domestic upheaval and the passage of time may indicate that reversal is required. Our studies show that when persistent azoospermia or severe oligozoospermia follows failure of vasectomy reversal, the scrotum should be re-explored to establish the cause of the failure. We have suggested a system of categorisation and indicated appropriate lines of treatment.

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The Authors

M. G. Royle, FRCS, Consultant Urological Surgeon, Royal Sussex County Hospital.

W. F. Hendry, ChM, FRCS, Consultant Urological Surgeon, St Bartholomew's Hospital.

Requests for reprints to: W. F. Hendry, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Pre-natal Diagnosis: How Useful is it?*

D. F. M. THOMAS, H. C. IRVING and R. J. ARTHUR

Departments of Paediatric Surgery and Diagnostic Radiology, St James's University Hospital and General Infirmary, Leeds

Summary—Dilatation of the fetal urinary tract can now be detected by ultrasound imaging in pregnancy. Forty-six cases of pre-natally diagnosed dilatation were analysed to assess the contribution of this information to subsequent urological management.

Positive pre-natal scans proved accurate. Dilatation was confirmed by neonatal ultrasound imaging or by autopsy in 24 of 25 consecutive inborn neonates and two aborted fetuses.

Forty-four live births were studied. Twelve neonates had physical signs at birth which rendered the pre-natal diagnosis unnecessary. In 32 neonates (73%) the urinary tract anomaly was identified solely as a result of pre-natal imaging and would otherwise have remained undetected. However, in seven neonates the information was of doubtful value (mild unilateral dilatation), in 16 it was of probable value (confirmed unilateral PUJ obstruction, multicystic kidney, *etc.*) and in only nine neonates (20%) was it of definite value (treatable conditions affecting both kidneys or a solitary kidney, *e.g.* urethral valves, PUJ obstruction in a solitary kidney, *etc.*).

Pre-natally detected bilateral dilatation (18 infants) carried a poor prognosis—33% mortality and 56% incidence of coexistent abnormalities. No infants in our series had undergone intra-uterine drainage, but the numbers of survivors and their renal function was comparable to the published results for fetal intervention.

Abnormalities of the fetal urinary tract are relatively common and may result in hydronephrosis which is often clearly visualised by routine ultrasound imaging in pregnancy. This report is a critical assessment of the current value of pre-natal urological diagnosis, its accuracy, capacity to detect unsuspected abnormalities and its contribution to clinical management.

Patients and Methods

The study covers a period of 33 months (August 1982 to April 1985). Thirty-one cases of fetal uropathy (subsequently confirmed following delivery) were detected on routine pre-natal ultrasound scanning in the two large obstetric units in Leeds. A further 15 neonates with pre-natally diagnosed hydronephrosis were referred from district hospitals in the Yorkshire Region. Termination of pregnancy was undertaken in two cases of gross bilateral hydronephrosis associated with maternal oligohydramnios before the twentieth week of gestation. Gross renal dysplasia was subsequently confirmed histologically in both cases. Intra-uterine drainage (fetal surgery) was not attempted in any case. Upper tract dilatation was confirmed after delivery and investigated further in 44 live born infants.

Results

Incidence Of 31 affected inborn neonates, six were shown to have a minor degree of unilateral dilatation, whilst 25 had a significant urological abnormality. This represents a current detection rate of approximately one significant urological abnormality for every thousand pregnancies. No attempt has been made to quantify the comparable detection rate for other hospitals in the Region.

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* Awarded the Eschmann Prize for the best paper presented at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Accuracy Positive pre-natal findings were confirmed in 24 of 25 consecutive inborn neonates in Leeds. The exception was one neonate with a pre-natal diagnosis of mild unilateral dilatation in whom post-natal scans demonstrated an entirely normal urinary tract. The number of urological abnormalities undetected by pre-natal imaging will not become evident for some years, but three cases have already come to light—one with posterior urethral valves and two infants with renal aplasia or gross dysplasia.

Relevance to Diagnosis and Management In 12 of the 44 live born neonates, the initial clinical findings alone would have led to the early discovery of a urological abnormality (Table 1). In 32 neonates (73%), however, no physical signs or stigmata of renal disease were present. This group has been further subdivided according to the relevance of the pre-natal diagnosis to clinical management and possible prognosis.

Table 1 Clinical Presentation

44 neonates	32 (73%)	Urological abnormality identified solely by pre-natal imaging	
	12 (27%)	Relevant clinical signs present	
		Abdominal mass and pulmonary hypoplasia	5
		Abdominal mass, no pulmonary hypoplasia	3
		Rectal atresia	1
		Lipomeningocele	1
		Down's syndrome	1
		Noonan's syndrome	1

Group A—pre-natal diagnosis of definite value (Table 2). In 10 neonates (23% of the total) the pre-natal imaging revealed otherwise unsuspected pathology affecting both kidneys or a solitary kidney. Thus the pre-natal information was thought to have been of definite value. Two children in this group (both with gross bilateral vesicoureteric reflux) had severe abnormalities affecting other systems, but eight were normal infants apart from their uropathy.

Group B—pre-natal diagnosis of probable value. Investigation of16 neonates (36% of the total) confirmed the presence of significant upper tract obstruction, multicystic kidney or vesicoureteric reflux occurring unilaterally. Pre-natal imaging was thought to have been of some value by identifying salvageable obstructed kidneys or those at risk from reflux scarring. Antibiotic prophylaxis has been instituted promptly whenever this has been appropriate and no child in this group has yet suffered a symptomatic urinary infection.

Table 2 Urological Abnormalities Detected Solely by Pre-natal Ultrasound

Group A	*Pre-natal diagnosis of definite value*	
	Posterior urethral valves	4
	Bilateral pelviureteric junction obstruction	2
	Pelviureteric obstruction with contralateral multicystic kidney	1
	Vesico ureteric reflux (bilateral)	2
	Vesicoureteric reflux (solitary kidney)	1
		10 (23%)
Group B	*Pre-natal diagnosis of probable value*	
	Unilateral pelviureteric junction obstruction	6
	Vesicoureteric junction obstruction	1
	Upper pole duplex obstruction	2
	Multicystic kidney	3
	Unilateral vesicoureteric reflux	4
		16 (36%)
Group C	*Pre-natal diagnosis of doubtful value*	
	Mild unilateral dilatation with normal MCU	6 (14%)
	Total	32 (73%)

Group C—pre-natal diagnosis of doubtful value. In six neonates the pre-natal diagnosis of mild unilateral dilatation was confirmed following delivery and reflux has been excluded as a possible cause. These children are being managed by serial ultrasound follow-up without, as yet, investigation by dynamic isotope renography or treatment with antibiotic prophylaxis. None has shown any increase in dilatation or loss of cortical thickness to suggest active obstruction.

Bilateral Fetal Uropathy The outcome of this group of untreated fetuses with bilateral uropathy has been analysed in some detail to permit comparison with the published results for fetal surgery. Two pregnancies were terminated. The histological findings were of renal and pulmonary dysplasia inconsistent with survival. The outcome for 18 live born neonates is detailed in Tables 3 and 4. In 10 neonates (56%) the uropathy was part of multi-system pathology. There were six deaths

Table 3 Bilateral Fetal Uropathy (18 Neonates)

Associated anomalies	
Pulmonary hypoplasia	5
Hydrocephalus, multiple abnormalities	1
Down's syndrome	1
Beckwith syndrome	1
Robinow syndrome	1
Noonan's syndrome	1
	10 (56%)

Table 4 Bilateral Fetal Uropathy: Outcome (18 Neonates)

6 Deaths—	5 early (pulmonary hypoplasia)	
	1 late (cot death/multiple anomalies)	
12 Survivors—	4 impairment of renal function	
	4 adequate renal function, but other serious abnormalities	
	4 adequate renal function, no other serious abnormalities	
	i.e. Bilateral PUJ obstruction	2
	Urethral valves	1
	Unilateral PUJ/unilateral multicystic	1

(33%), five from pulmonary insufficiency in the first few days of life, the sixth a cot death at 1 year in a child with multiple anomalies. Four of the survivors have had biochemical evidence of impaired renal function, whilst eight have had normal plasma values for urea and creatinine throughout. However, of the eight children with adequate renal function, four have severe associated anomalies or syndromes. Thus, despite pre-natal diagnosis and prompt *ex utero* treatment, only four of 18 infants have a good prognosis for normal development and renal function.

Discussion

Pre-natal diagnosis is likely to have an increasing impact on paediatric urological practice. This study suggests that the incidence of pre-natally diagnosable abnormalities is at least one per thousand live births. Although the overall pre-natal detection rate will be dependent upon the prevalence and accuracy of ultrasound imaging in district hospitals, the average Region could be expected to yield between 30 and 60 cases per year. The volume and complexity of the work generated by pre-natal diagnosis is a powerful argument for the recognition of paediatric urology as a regionally based specialty. Our findings add weight to those already published by Turnock and Shawis (1984), who analysed 29 cases of fetal uropathy diagnosed over 3½ years in Liverpool. These authors noted that one-third of affected neonates had relevant physical signs at birth, whereas in two-thirds the abnormality was clinically undetectable. These authors have also categorised the information as being of definite, probable or no benefit—with results broadly comparable to ours.

Pre-natal imaging is most effective in identifying unilateral lesions—of which in this series only 11% were clinically detectable. With the exception of pathology affecting solitary kidneys, the information is not of direct relevance to survival or, necessarily, to long-term renal function. Our management of pre-natally diagnosed PUJ obstruction has been largely in accordance with the criteria suggested by Ransley and Manzoni (1985). Like these authors, we have found a period of percutaneous nephrostomy drainage to be a useful predictor of recovery in poorly functioning obstructed kidneys.

The case for removing asymptomatic multicystic kidneys is arguable and, for the time being, we continue to do so, but not before 6 months of age. The demonstration of vesicoureteric reflux in seven neonates (22% of neonates with clinically undetectable dilatation) suggests that a micturating cystourethrogram should be undertaken as a routine even when the initial post-natal ultrasound imaging reveals only minimal dilatation or "splitting of the calices".

There is general agreement that intra-uterine surgery has no place in the management of unilateral fetal uropathy. Our results suggest that, for the present, these reservations should apply equally to bilateral fetal uropathy. None of the 18 neonates in this series was treated by intra-uterine drainage, yet the outcome, both in terms of percentage survival and preservation of renal function in the survivors, is comparable to published results following fetal surgery (Harrison *et al.*, 1982; McFayden, 1984). Deaths from pulmonary hypoplasia cannot be prevented by early intra-uterine drainage, nor can dysmorphic fetuses (for whom intra-uterine surgery would be inappropriate) be excluded from treatment. There is no evidence to suggest that a fetus with bilateral PUJ obstruction or non-obstructive dilatation would benefit from drainage. With current technology, the small minority of fetuses (mainly with urethral valves) for whom a case for intra-uterine drainage might be argued, cannot be distinguished from the majority for whom such intervention would be ineffective or inappropriate.

Pre-natal diagnosis is a new and fascinating aspect of paediatric urology, but the clinical applications of pre-natal imaging should be kept under continuing and critical review.

Acknowledgements

We are indebted to Dr J. Watters and Dr M. Bark (Consultant Radiologists) and to the Consultant Obstetricians and Paediatricians in Leeds and the Yorkshire Region who have generously allowed us to study their patients.

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The Authors

D. F. M. Thomas, MA, MRCP, FRCS, Consultant Paediatric Surgeon/Urologist.
H. C. Irving, FRCR, Consultant Radiologist.
R. J. Arthur, MRCP, FRCR, Consultant Paediatric Radiologist.

Requests for reprints to: D. F. M. Thomas, Department of Paediatric Surgery, Clarendon Wing, General Infirmary, Belmont Grove, Leeds LS2 9NS.

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The Outcome of Antenatally Diagnosed Urological Abnormalities

R. D. POCOCK, J. B. WITCOMBE, HEATHER S. ANDREWS, P. J. BERRY and J. D. FRANK

Departments of Paediatric Urology and Pathology, Royal Hospital for Sick Children, Bristol; Departments of Radiology, Gloucestershire Royal Hospital, Gloucester and Bristol Maternity Hospital, Bristol

Summary—Twenty-eight patients undergoing routine antenatal screening by ultrasound were found to have a fetus with a major urological abnormality. In addition, two babies suspected of having an enlarged bladder were found post-natally to be normal. Seven of the 28 pregnancies were terminated before 26 weeks' gestation as a result of the ultrasound findings and all these fetuses had lethal renal abnormalities. Of the remaining 21 babies, four died of renal failure following delivery. Fifteen of the 17 babies who are alive and well had an ultrasound scan before 24 weeks' gestation. Only one of these scans revealed the abnormality. In the remaining patients the abnormality was first detected after 28 weeks. No patient had surgery *in utero*. Our data suggest that renal abnormalities detected prior to 24 weeks' gestation are associated with severe renal impairment. It appears that the role of antenatal drainage procedures may be of limited value.

Many centres screen all pregnant mothers by ultrasound examination between 16 and 20 weeks. This provides useful data for determining gestational dates but may also reveal fetal abnormalities, many of which are urological (Hutson *et al.*, 1985). Ultrasound examinations in the third trimester are usually performed for obstetric reasons but again fetal abnormalities may be detected.

The detection of these abnormalities leads to difficult management decisions for the clinicians involved. Does the detection of severe abnormalities in the second trimester justify termination of the pregnancy? Does antenatal drainage of the obstructed urinary tract preserve sufficient renal function to sustain normal life after birth? Finally, should asymptomatic babies with relatively minor abnormalities such as a unilateral pelviureteric junction obstruction be managed post-natally by surgery or conservatively, as some authors have advocated (Ransley and Manzoni, 1985)? If surgery is indicated, at what age should this be performed?

Patients and Methods

Twenty-three babies were referred to the Bristol Royal Hospital for Sick Children between September 1982 and June 1985 with a urological abnormality detected antenatally by ultrasound examination. Seven further patients had their pregnancies terminated on the basis of these findings and the fetuses referred for pathological examination. Twenty-three patients came from Bristol and Gloucester, the remainder from four centres in the South-west region. It is a policy in all but one of these centres to perform ultrasound scans on all pregnant women between 16 and 20 weeks. Ultrasound scans in the third trimester were performed for obstetric reasons or to follow up a possible fetal abnormality.

The final diagnosis was made by an intravenous urogram, post-natal ultrasound, isotope studies and a cystogram where indicated or by *post mortem* examination. In no case was an antenatal drainage procedure attempted.

Results (Table 1)

The ultrasound examination correctly diagnosed

Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Table 1 Results

		Timing (weeks)			
	Sex	*Early U/S*	*Abnormality detected*	*U/S diagnosis*	*Final diagnosis*
Late alive and well					
1.	M	20	37	R. multicystic kidney	R. multicystic kidney
2.	F	16	39	Large bladder	Normal
3.	M	17	37	L. hydronephrosis	L. PUJ obstruction
4.	F	16/18	28	R. hydronephrosis	R. PUJ obstruction
5	M	37	37	Bilat. hydronephrosis	Bilat. PUJ obstruction
6.	M	15/21	36	Bilat. hydronephrosis	Bilat. PUJ obstruction
7.	M	16/22	28	L. hydronephrosis	Bilat. obstructing megaureter
8.	F	17/27	34	R. hydronephrosis	R. PUJ obstruction
9.	M	16	32	Bilat. hydronephrosis	Bilat. PUJ obstruction
10.	F	17/19	29	R. hydronephrosis	R. multicystic kidney
11.	M	18	33	R. hydronephrosis and hydroureter	R. megaureter
12.	M	23	34	Cystic areas in both kidneys	L. PUJ obstruction
13.	F	16	26	L. multicystic kidney	L. multicystic kidney
14.	M	16	32	Bilat. hydronephrosis	Bilat. mild negaureter
15.	M	16	34	L. hydronephrosis	L. PUJ obstruction
16.	M	28	31	Large liver and kidneys	Beckwith's syndrome
17.	M	16	34	L. multicystic kidney	L. multicystic kidney
Late died post-delivery					
18.	F	37	37	Bilat. hydronephrosis	Bilat. obstructed megaureters
19.	M	30	30	Bilat. hydronephrosis and hydroureter	Urethral atresia
Early alive and well					
20.	M	16	16	Large bladder	Normal
21.	F	21	21	L. hydronephrosis	L. obstructing ectopic ureterocele
Early died post-delivery					
22.	M	20	20	Oligohydramnios Polycystic kidneys No bladder	Multicystic kidneys
23.	M	16/20	16	Pelvic cyst Kidneys not seen ?Prune belly	Urethral valve/atresia
Early terminated					
24.	F	20/25	25	Oligohydramnios Multicystic kidneys No bladder	Multicystic dysplastic kidneys Bilat. ureteric atresia Imperforate anus Vertebral abnormalities Cardiac malformation
25.	F	23	23	Oligohydramnios No bladder Renal agenesis Hydrocephalus	Renal agenesis Holoprosencephaly
26.	M	17	17	Oligohydramnios No bladder Cystic kidneys	Solitary cystic dysplastic kidney
27.	M	16/18/20	16	Oligohydramnios No bladder Renal agenesis	Single pelvic dysplastic kidney
28.	M	16/18	16	Bilat. hydronephrosis Hydrocephalus	Bilat. PUJ obstruction No renal tissue No eyes Trisomy
29.	F	16/18	16	Oligohydramnios Hydronephrosis Large bladder (Progressed between scans)	Obstructed cloacal abnormality Multicystic/dysplastic kidneys
30.	M	16/17	16	Oligohydramnios Cystic kidneys	Urethral atresia Unilateral ureteric atresia

an abnormality in all but four patients. In two babies (nos 2 and 20) the bladder was considered to be enlarged. After birth both babies were clinically normal and this was confirmed by a normal intravenous urogram and cystogram. The ultrasound examination failed to diagnose the abnormality as bilateral in patient no. 7 and gave a false positive diagnosis of bilateral disease in no. 12. However, significant urological disease was present in both babies. In all pregnancies where a termination was performed on the basis of a major urological abnormality with associated oligohydramnios or hydrocephalus, the *post mortem* examination confirmed that the abnormality was incompatible with life (Fig. 1). In two patients the antenatal diagnosis helped in the subsequent management. In patient no. 16 (Beckwith's syndrome), early glucose therapy was instigated. In patient no. 21 the cause of the hydronephrosis was shown soon after delivery to be an ectopic ureterocele. The parents declined surgical intervention. At 3 months of age the baby became severely ill with a urine infection and hyponatraemia. After initial resuscitation, early surgery (upper pole heminephrectomy) was undertaken without the need for further investigations.

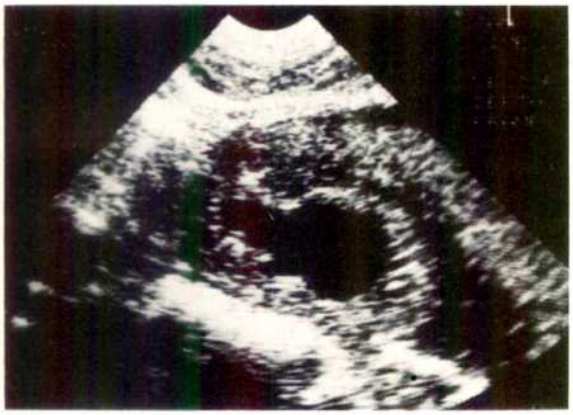

Fig. 1 Coronal scan in patient no. 29 at 16 weeks showing oligohydramnios, dilated bladder and urethra.

Fifteen of the 17 patients who remain alive and well had an ultrasound scan prior to 24 weeks' gestation. Fourteen of these early scans were normal, the abnormality being detected in one (patient no. 21). In the remainder the abnormality was not detected until after 26 weeks (Fig. 2). Four patients (nos 18, 19, 22, 23) died after delivery with renal failure as the major cause of death. Only one patient in this group (no. 23) had an obstructive uropathy diagnosed early. The other two (nos 18 and 19) presented late. One went to term, the other going into spontaneous labour at 34 weeks. In none of these patients was antenatal surgery considered by the referring hospital.

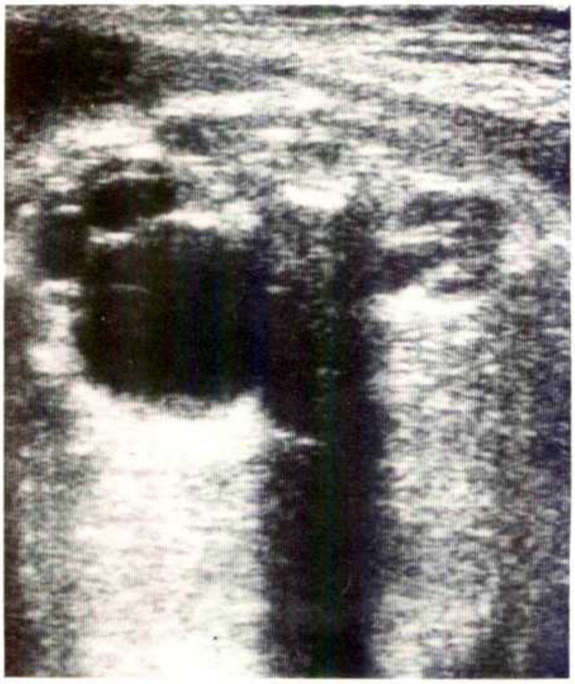

Fig. 2 Transverse scan of patient no. 3 showing unilateral pelviureteric junction obstruction.

Table 2 shows the subsequent treatment given to the babies.

Discussion

These results show that antenatal ultrasound examination accurately diagnoses fetal urological abnormalities. It is not possible to identify the number of false negative examinations, as this would require a post-natal examination of the urinary tract of every baby with a normal antenatal scan. However, in our institution no lethal urological abnormality has been missed by antenatal ultrasound examination. There were only two false positive examinations, in which a large bladder was noted but the upper tracts were normal.

The abnormalities fell into two groups, with one exception (patient no. 21). Firstly, there were those patients in whom the abnormality was detected before 24 weeks' gestation who had severe renal impairment incompatible with life. Figure 3 shows such a patient (no. 30) who was aborted at 17 weeks and in whom a positive scan was first noted

Table 2 Antenatal Diagnosis and Follow-up

Patient No.	*DOB*	*Diagnosis*	*Treatment*
1	08.11.83	R. multicystic kidney	R. nephrectomy
3	02.10.84	L. PUJ obstruction	L. pyeloplasty
4	02.11.83	R. PUJ obstruction	R. pyeloplasty
5	26.10.82	Bilat. PUJ obstruction	Bilat. pyeloplasty
6	30.08.83	Bilat. PUJ obstruction	Bilat. pyeloplasty
7	22.08.83	Bilat. megaureter	Bilat. reimplant
8	31.01.84	R. PUJ (non-functioning kidney)	Conservative
9	08.09.84	Bilat. PUJ	Bilat. pyeloplasty
10	17.04.83	R. multicystic kidney	R. nephrectomy
11	19.03.85	R. megaureter	Conservative
12	01.06.83	L. PUJ	L. pyeloplasty
13	02.08.83	L. multicystic kidney	Conservative
14	23.12.84	Bilat. megaureter (mild)	Conservative
15	14.05.85	PUJ	Conservative
16	03.02.85	Beckwith's syndrome	Medical management
17	30.07.84	L. multicystic kidney	Conservative
18	17.01.83	Bilat. megaureters	None (died 24 h)
19	08.11.84	Urethral atresia	None (died 5 h)
21	25.03.84	L. ectopic ureterocele	L. upper pole heminephrectomy
22	20.08.84	Multicystic kidneys	None (died 24 h)
23	07.11.84	Urethral valve	Vesicostomy (died 3/52)

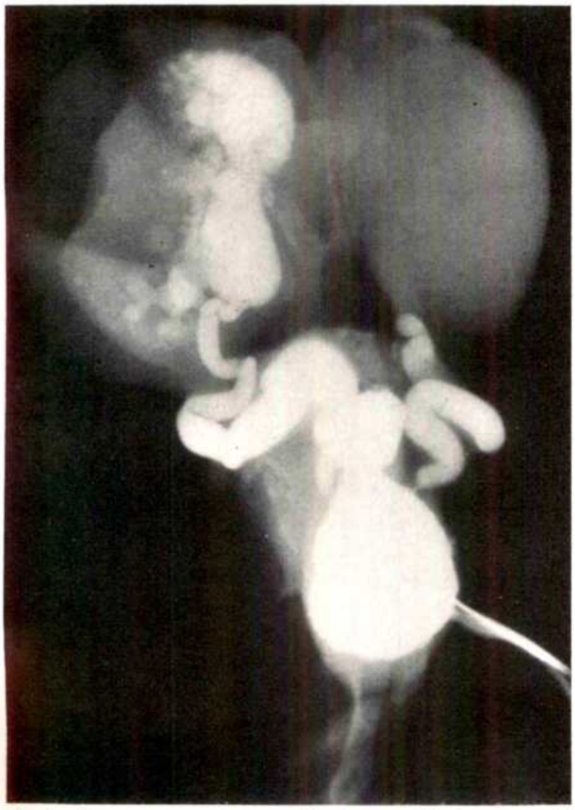

Fig. 3 *Post mortem* cystogram of patient no. 30 showing urethral and unilateral ureteric atresia.

at 16 weeks. The obstruction from the posterior urethral valve had already caused complete loss of functioning renal tissue. It is probable that urinary obstruction occurring during the early development of the metanephros (8 weeks onwards) leads to the severe renal impairment. It is surprising that in this fetus and others, obstruction of the outflow tract did not lead to the persistence of a patent urachus as is seen in the animal model (Harrison *et al.*, 1983). If this renal damage occurs early in gestation and is irreversible, it would explain the poor results seen with *in utero* surgery (Harrison *et al.*, 1982). It is also possible that some children who have good renal function following antenatal drainage procedures would have done well without intervention, as seen in those of our patients diagnosed after 26 weeks' gestation.

Only three of our patients might have been helped by *in utero* drainage. However, two presented so late that this was impractical and in the third the referring hospital failed to follow up the initial ultrasound findings. We feel that in order to determine whether renal impairment is sufficient to justify *in utero* drainage and also to assess subsequent benefit, a technique to measure fetal renal function is required.

The second group of patients had good renal function and the abnormality was first diagnosed late (26–37 weeks). It is interesting that in 15 of 17 patients who had a scan performed prior to 24 weeks it was normal. To determine when the abnormality can first be detected, examinations at different times during pregnancy are required.

The post-natal management of these asymptomatic patients is controversial. It is our policy to carry out early corrective surgery in patients with bilateral disease. Patients with unilateral disease had the investigations repeated between 3 and 6 months after birth and a decision regarding surgery was then made. Clearly such management is at the moment empirical. We are aware that these abnormalities may not behave in the same way in these patients as in children who present with symptoms. There is a suggestion that some of these patients with an apparent obstructive uropathy may improve with conservative management (Ransley and Manzoni, 1985). Further work is needed to try to assess the natural history of these abnormalities and to determine the role and timing of surgery.

Acknowledgements

We thank the paediatricians and radiologists in the South-West region who referred these cases and also Sarah Jane Bryan for typing the manuscript.

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The Authors

R. D. Pocock, FRCS, Senior Urological Registrar, Bristol Royal Hospital for Sick Children.

J. B. Whitcombe, FRCR, Consultant Radiologist, Gloucestershire Royal Hospital.

Heather S. Andrews, MRCP, FRCR, Consultant Radiologist, Bristol Maternity Hospital.

P. J. Berry, MRCP, MRCPath, Consultant Paediatric Pathologist, Bristol Royal Hospital for Sick Children.

J. D. Frank, FRCS, Consultant Paediatric Surgeon and Urologist, Bristol Royal Hospital for Sick Children.

Requests for reprints to: J. D. Frank, Department of Paediatric Surgery, Bristol Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ.

British Journal of Urology (1985), **57**, 793-794

Point of Technique

Retrograde Insertion of Double Pigtail Stents: a More Reliable Technique

W. J. WALKER and R. G. NOTLEY, *Department of Urology, Royal Surrey County Hospital, Guildford.*

Double pigtail stents are usually inserted antegrade by radiologists and retrograde by urologists. It has been asserted that the former approach, although causing greater patient discomfort and inconvenience, is more consistently successful (Mardis *et al.*, 1982). This is probably due to two factors: (a) the employment of "angiographic" as opposed to "endo-urological" techniques for negotiation of the ureter, and (b) better "run-in" and alignment characteristics for cannulation of low ureteric strictures. However, it is important to realise that the former angiographic methods can also be

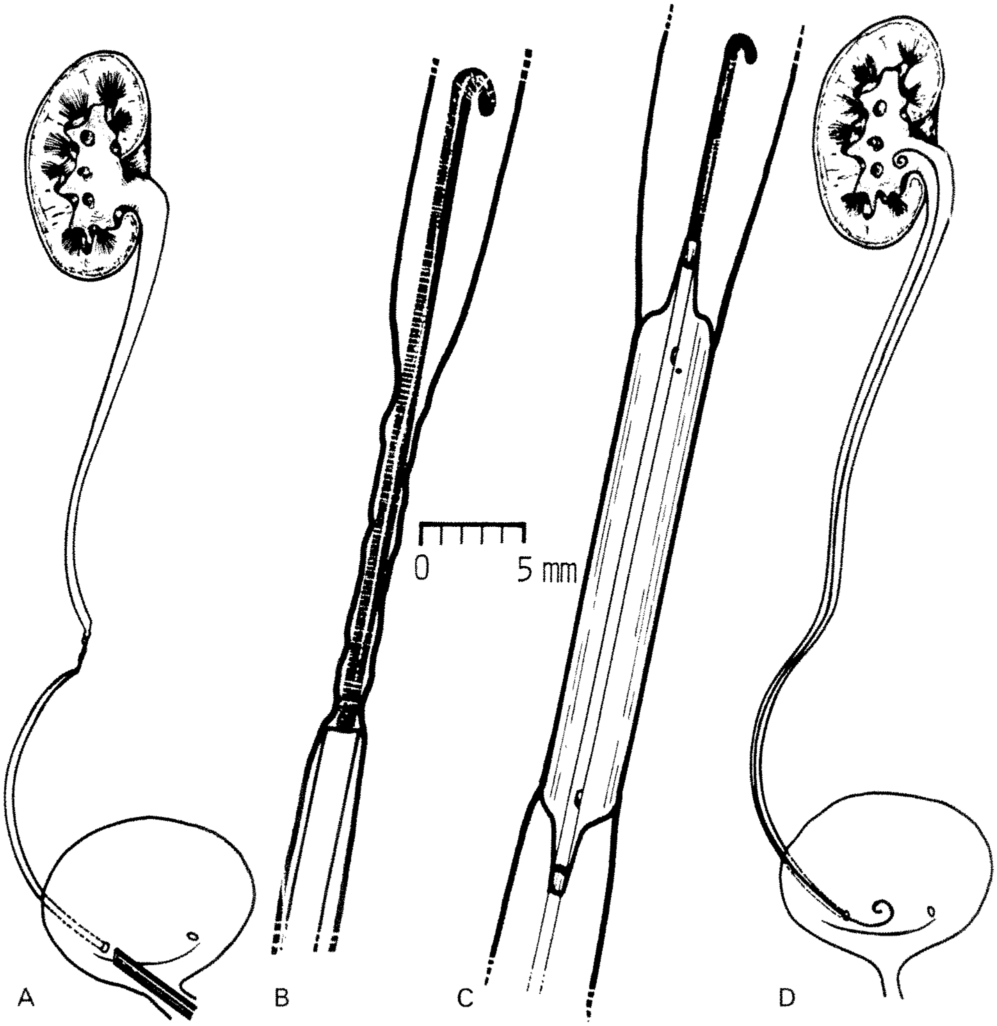

Fig. 1 (A) Endoscope placed at ureteric orifice. (B) Shaped catheter passed up to and just into occlusion. Contrast injected to demonstrate course of obliterated lumen and guide wire passed through obstruction into upper ureter. (C) Following dilatation with an 8 F Van Andel catheter the lesion is dilated with a 5 mm balloon catheter. (D) Under fluoroscopic control a double pigtail stent is inserted across the obstruction.

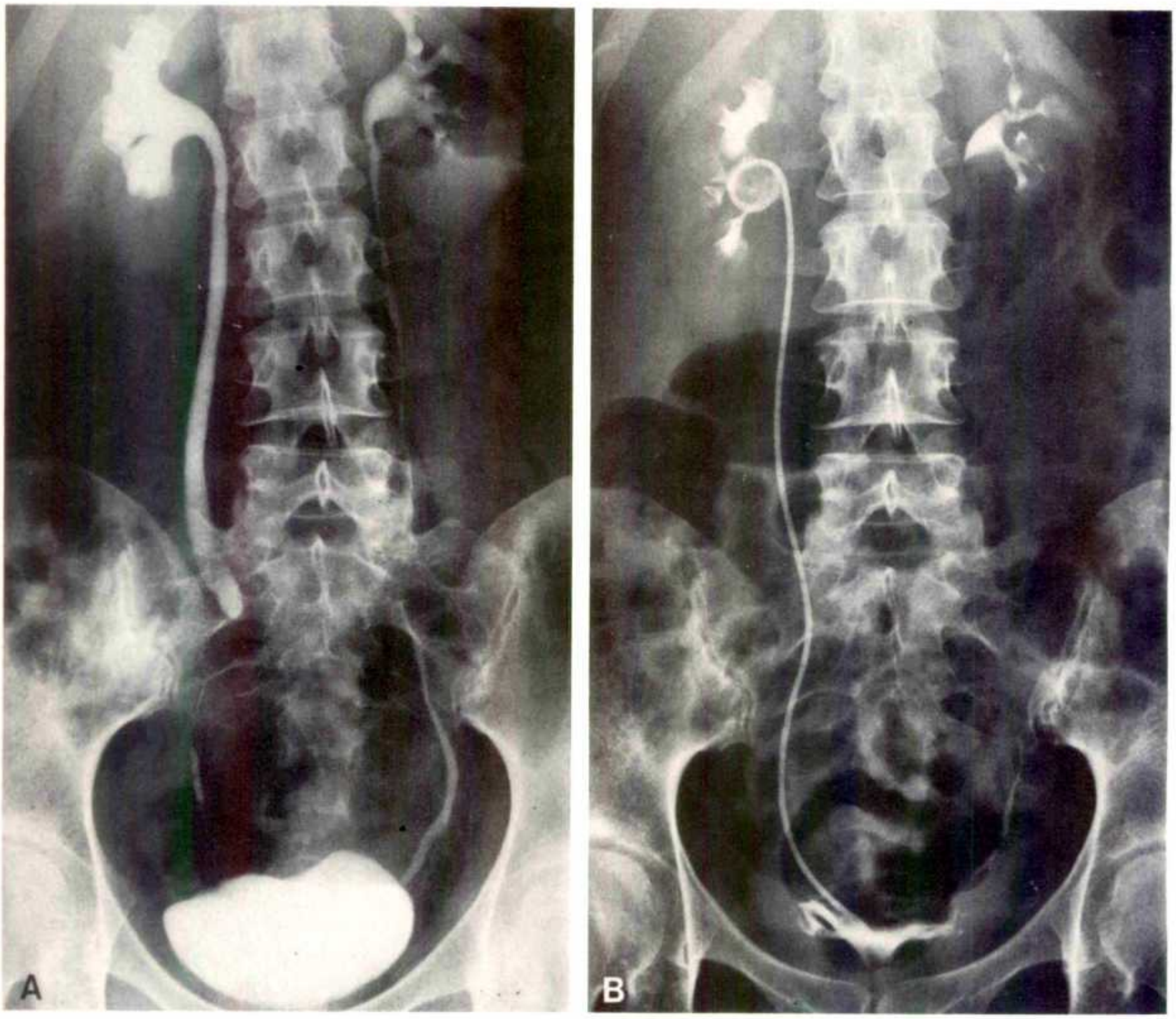

Fig. 2 (A) Malignant stricture distal right ureter. (B) Appearance after insertion of double pigtail stent.

employed from below if the joint co-operation of urologist and interventional radiologist is used.

Technique

The essential point of technique and prerequisite for success in both female and male patients is placement of the endoscope *at* the ureteric orifice, permitting a more direct transfer of movement of the external segment of catheter to its intra-ureteric portion. Then under fluoroscopic guidance and with the intermittent injection of contrast medium, guide wires, shaped catheters and angioplasty balloons can be used to cannulate the ureter as for routine angiography or angioplasty (Figs 1 and 2). We have used this method in five patients and believe it will greatly improve the success rate of retrograde ureteric catheterisation.

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Requests for reprints to: R. G. Notley, Department of Urology, Royal Surrey County Hospital, Guildford GU2 5XX.

Based on a Poster Demonstration at the 41st Annual Meeting of The British Association of Urological Surgeons in Eastbourne, July 1985

British Journal of Urology (1985), **57**, 795

The British Association of Urological Surgeons: Annual Meeting

President: J. P. Blandy, MCh, FRCS

Eastbourne, 9-12 July 1985

Prizes and Awards

St Peter's Medal

At the Annual Dinner the President presented the St Peter's Medal to Mr J. E. A. Wickham of the Institute of Urology and St Bartholomew's Hospital, London, after a citation given by Mr C. A. C. Charlton.

Bard Award

The Bard Silver Medal was awarded to Mr N. T. M. Galloway for the essay entitled "The occult neuropathic bladder".

Eschmann Prizes

The prize of £500 for the best paper presented at the Annual Meeting was awarded to Mr D. F. M. Thomas (with H. Irving and R. J. Arthur) for the paper entitled "Pre-natal diagnosis: how useful is it?"

The prize of £500 for the best poster was awarded to Mr J. W. A. Ramsay (with S. R. Payne, A. Murray, P. T. Gosling, H. N. Whitfield, W. F. Hendry and J. E. A. Wickham) for the poster entitled "Flow mechanics and internal urinary diversion: a clinical and experimental study of double J stents".

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000 for any article(s) of outstanding merit in each volume of the British Journal of Urology. Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia, or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to Urological Centres outside Britain for consideration by the Council.

The 1985 prize was awarded to Mr A. W. S. Ritchie for his contributions to Volume 56, 1984, entitled "Intra-epithelial lymphocytes in the normal epididymis. A mechanism for tolerance to sperm auto-antigens" (pp. 79-83) and "Lymphocyte subsets in renal carcinoma—a sequential study using monoclonal antibodies" (pp. 140-148).

DANTEC Prize

This prize is awarded for the best scientific paper contributing towards the understanding of urinary tract function which has been accepted by a medical journal for publication in the United Kingdom.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered.

The award for 1984 was given to Mr P. G. Ransley for the paper entitled "High pressure sterile vesicoureteral reflux and renal scarring: an experimental study in the pig and minipig" by P. G. Ransley, R. A. Risdon and M. L. Godley, *Contributions to Nephrology* (*Section VIII*), **39**, 320-343.

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MATERIAL BENEFITS-NOW AND FOR THE FUTURE.

Many more surgeons are joining the growing group of synthetic absorbable suture users, for very good reasons.

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TECHNICAL DATA OVERLEAF

TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Absorbable Synthetic Monofilament Suture

Presentation
PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C blue No 6 (gauge 0.2 metric and 0.3 metric) D&C violet No 2 (gauge 0.4 metric to 5 metric) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses
PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal mucosal sutures could cause localised irritation if left in place for longer than 10 days and should be removed as indicated. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiovascular tissue have not yet been established. The use of this material in the renal tract is currently under investigation.

Pharmaceutical Precautions
Do not resterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Packaging
The gauge range available will be 0.3 metric (9/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets.

The primary pack is sealed within a peel-apart secondary pouch and contained in a film-wrapped drawer style carton.

Further Information
So suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos PL 0508/0011 (dyed); PL 0508/0012 (clear).

Br Pat No 1 540 053.

Date of preparation of Data Sheet – September 1982.
Revised 1/1985.

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Absorbable Synthetic Braided Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses
Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissue under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardio-vascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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